96-169

ANTIBIOTICS IN ANIMAL FEED

HEARINGS

BEFORE THE

SUBCOMMITTEE ON
HEALTH AND THE ENVIRONMENT
OF THE
COMMITTEE ON
INTERSTATE AND FOREIGN COMMERCE
HOUSE OF REPRESENTATIVES
NINETY-SIXTH CONGRESS
SECOND SESSION
ON

H.R. 7285

A BILL TO AMEND THE FEDERAL FOOD, DRUG, AND COSMETIC ACT TO LIMIT THE ANTIBIOTIC DRUGS WHICH MAY BE USED IN SUBTHERAPEUTIC DOSES IN ANIMAL FEED

JUNE 12 AND 24, 1980

Serial No. 96–169

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Committee on Interstate and Foreign Commerce

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American Academy of Sciences, Reuel A. Stallones, M.D.

American Medical Association:
- Cahill, Nancy, department of Federal legislation.
- Crocco, Stephanie, Ph. D., food scientist, department of foods and nutrition.
- Finkel, Asher J., M.D., group vice president for scientific affairs.

American Society for Animal Sciences, Willard J. Visek, M.D., Ph. D.

Animal Health Institute, Eugene Lambert, counsel.

Health and Human Services Department, Lester M. Crawford, D.V.M., Ph. D., Director, Bureau of Veterinary Medicine, Food and Drug Administration, Public Health Service.

Office of Technology Assessment, Joyce C., Lashof, M.D., Assistant Director, Health and Life Sciences Division

ANTIBIOTICS IN ANIMAL FEED

THURSDAY, JUNE 12, 1980

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON HEALTH AND THE ENVIRONMENT,
COMMITTEE ON INTERSTATE AND FOREIGN COMMERCE,
Washington, D.C.

The subcommittee met, pursuant to notice, at 11 a.m., in room 2237, Rayburn House Office Building, Hon. Henry A. Waxman, chairman, presiding.

Mr. **WAXMAN**. The meeting will come to order.

The Subcommittee on Health and the Environment is holding hearings today on H.R. 7285, the Antibiotics Preservation Act. I believe this bill addresses one of the most serious public health matters this subcommittee has faced.

Antibiotics are some of the most important human drugs ever developed, but now many of the antibiotics of choice for humans are being used to promote growth and improved feed efficiency in pigs, chickens, and cows. The use of medicated animal feed is widespread and it now appears that it could be a major cause of increasing human resistance to antibiotics. The use of human antibiotics in animal feeds is particularly distressing because we have other drugs which could be substituted for them.

Because of my desire to assure the continued efficacy of antibiotics in humans, I have joined with our distinguished colleague, Congressman John Dingell, in sponsoring H.R. 7285. This bill would authorize FDA to restrict the use of certain human antibiotics in animal feed in subtherapeutic amounts. Subtherapeutic amounts are those at which the dose given an animal is too small to treat disease. Many livestock producers believe that the use of antibiotics at subtherapeutic levels prevents the outbreak of disease and promotes growth and feed efficiency. I wonder about the validity of this argument and whether it justifies a practice which is a compensation for poor animal management instead.

The science of antibiotic resistance in humans is clear. We are seeing increased human resistance to certain antibiotics. We know that resistance can be transferred from animals to humans. Scientists and physicians are predicting major health problems in the relatively near future, if antibiotic resistance continues to increase. Some drugs such as penicillin and tetracycline may no longer be available to us for treatment of human disease. The question is: Can we afford to lessen or to eliminate the effectiveness of these important human antibiotics? Although we cannot determine how much resistance is due to methods of livestock production, we know they are contributors. Good public policy would appear to favor restricting the subtherapeutic use of human antibiotics in animal

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feeds. For this reason, Congressman Dingell and I have introduced this bill, H.R. 7285, and believe it is time for congressional action.

Before I call upon our colleague Mr. Dingell for his opening statement in support of this legislation, I would like to recognize the distinguished ranking Republican member of this subcommittee, Dr. Tim Lee Carter.

Mr. **Carter**. Mr. Chairman, first I want to commend you and our distinguished colleague, Mr. Dingell, for introducing this legislation. I believe that the use of antibiotics in animal feed is an important issue, one which may involve serious negative consequences to the public's health and one which deserves serious discussion and scrutiny by this subcommittee. However, as is so often the case in dealing with public health issues, the evidence concerning the risk to human health in the use of antibiotics in animal feeds is far from clear.

For example, the National Academy of Sciences noted that postulated hazards to human health were neither proven nor disproven by their study. That study also pointed out that no data exist to establish the relationship between illness caused by an antimicrobial-resistant pathogenic effect bacteria and contacts with animals or meat from animals given only subtherapeutic amounts of antibiotics. Nevertheless, there is a mounting concern about the possible effects of the continued use of antibiotics in animal feeds. Clearly, we can't ignore this concern and we can't ignore the concerns raised by the Office of Technology Assessment.

It is because of this concern that I am pleased that these hearings have been scheduled on the Dingell-Waxman bill. I believe that it is appropriate and important that we explore this issue in a rigorous and equitable fashion, taking into account the possible threat to human health, and I say possible, but also considering the impact on the consumer and the producer of mandating changes in animal feeding practices.

We know, Mr. Chairman, over the years that bacteria become resistant to antibiotics even when taken by humans, and by humans alone. We have noticed this over the years. Certain strains, staphylococcus in particular, become resistant to penicilin, even though the human has never taken it or is given limited doses of antibiotics, or beef or chicken, which were also fed these things. When it was first used in the last part of 1943, although it had been discovered I believe by Flemming in 1927, penicillin was a miracle drug, but even then resistance of bacteria developed.

Furthermore, it is known that animals fed these antibiotics do grow more rapidly and are free from disease.

Thank you, Mr. Chairman.

Mr. **Waxman**. Thank you very much, Dr. Carter.

Without objection, the text of H.R. 7285 will be printed at this point in the record.

[The text of H.R. 7285 follows:]

I

96th CONGRESS
2d Session

H. R. 7285

To amend the Federal Food, Drug, and Cosmetic Act to limit the antibiotic drugs which may be used in subtherapeutic doses in animal feed.

IN THE HOUSE OF REPRESENTATIVES

May 7, 1980

Mr. Dingell (for himself and Mr. Waxman) introduced the following bill; which was referred to the Committee on Interstate and Foreign Commerce

---

A BILL

To amend the Federal Food, Drug, and Cosmetic Act to limit the antibiotic drugs which may be used in subtherapeutic doses in animal feed.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled, That this Act may be cited as the "Antibiotics Preservation Act".

Sec. 2. The Congress finds—

(1) those antibiotics, particularly penicillins and tetracyclines, which are the drugs of choice for use in humans against numerous infectious diseases are also

the primary antibiotics for use in animal feeds in subtherapeutic amounts;

(2) the continuous use of these and other antibiotics in subtherapeutic amounts has resulted in the development of pathogenic bacteria in animals that are singly and multiply resistant to such antibiotics;

(3) such pathogenic bacteria are then transmitted to humans where they colonize and cause diseases (such as meningitis, gonorrhea, and salmonellosis) for which there is virtually no effective antibiotic treatment;

(4) the Office of Technology Assessment in its report, "Drugs in Livestock Feed", concluded that the health risk to humans from the development of pathogenic bacteria resistant to antibiotics is greater than the risk of cancer presented by the use of diethylstilbestrol (DES) in animal feed;

(5) to avoid this risk to human health several Western European countries have for a number of years restricted the use of antibiotics in subtherapeutic amounts in animal feed; and

(6) the adoption of such a restriction in this country will protect the public health by preserving the efficacy of human antibiotics and will not hinder the raising of livestock because there are numerous approved

substitutes for the human antibiotics currently used in animal feeds.

SEC. 3. (a)(1) Section 507 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 357) is amended by adding at the end the following:

"(i) To provide reasonable assurance of the continued effectiveness in humans of antibiotic drugs, the Secretary shall designate, by regulation, antibiotic drugs which may not be used in subtherapeutic doses (as defined in such regulation) in animal feed or in ingredients of animal feed. The Secretary may, upon application and by order, authorize the use of an antibiotic drug designated under this subsection in an animal feed or in ingredients of an animal feed if the Secretary determines such use is required to meet a compelling need.".

(2) Not later than one hundred and eighty days after the date of the enactment of this Act, the Secretary of Health, Education, and Welfare shall first promulgate the regulation prescribed by section 507(i) of the Federal Food, Drug, and Cosmetic Act designating antibiotic drugs which may not be used in subtherapeutic doses in animal feed or in ingredients of animal feed.

(b) Section 501(a)(1) of such Act (21 U.S.C. 351(a)(1)) is amended by inserting before the period the following: "; or (7) if it is an animal feed or an ingredient of an animal feed

bearing or containing in subtherapeutic doses an antibiotic drug designated under section 507(i) and the use of the drug has not been authorized by an order issued under such section".

○

Mr. WAXMAN. Mr. Dingell, we want to welcome you to the committee today. We are pleased to have you with us and to hear your remarks.

STATEMENT OF HON. JOHN D. DINGELL, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MICHIGAN, ACCOMPANIED BY RICHARD C. FORTUNA, LEGISLATIVE ASSISTANT

Mr. DINGELL. Mr. Chairman, I thank you and the distinguished subcommittee for the opportunity to appear before you. I am accompanied this morning by Mr. Richard C. Fortuna of my staff. I thank you specifically for your cosponsorship and for your granting of the hearing on this important measure of antibiotic ineffectiveness.

Your abiding concern for the health of the American people is matched only by your extraordinary leadership and personal prowess in this most engaging of policy arenas.

Mr. Chairman, I would like to take this opportunity also to recognize the esteemed ranking minority member of the subcommittee, my good friend Dr. Tim Lee Carter, for whom I have the greatest affection and whose departure I view with a great deal of distress. His contributions to the Nation's health policy for the past 16 years are legion. Both the country and the Congress owe Dr. Carter a debt of gratitude that words can only approximate.

Last, Mr. Chairman, I salute all members of the subcommittee for the tenacity they have shown through many an arduous debate during this Congress over vital questions relating to the national health. You have served the Nation well and may indeed be proud of your contributions. But, despite our habit for partitioning the Nation's crises into 2-year intervals, there are some issues whose very nature commands the immediate concern and attention of each and every one of us regardless of its place on the legislative calendar.

The ominous specter of antibiotic ineffectiveness and its untoward impact on public health and clinical treatment demand that we immediately enact legislation to protect and preserve the therapeutic efficacy and lifesaving value of antibiotics.

Parenthetically, Mr. Chairman, I am probably in this room because years ago when a meningicoccal epidemic spread through the camp at which I was stationed, Camp Blanding, penicillin was not only available but effective as well, and indeed the level of bacterial resistance to penicillin to which Dr. Carter referred had not yet been achieved in the general population.

For the reasons that I have mentioned above, I have introduced with the distinguished subcommittee chairman, Mr. Waxman, H.R. 7285, the Antibiotics Preservation Act. The intent of the bill is clear and basic and speaks to the utmost level of commonsense within us—remove human therapeutic antibiotics from animal feed, and replace them with any one of the antibiotics currently approved specifically and solely for use in animal feeds.

For decades, the Nation has witnessed the declining efficacy of clinically important antibiotics, particularly penicillins and tetracyclines. Antibiotics that once hailed an era of miracle cure now stand as the hallmark of an age of antibiotic abuse and ineffectiveness. The medical literature is rife with examples of this decline, and I would commend these to my colleagues:

Tetracycline, once highly effective in treating the life-threatening disease of cholera, is now a severely compromised regimen. (CDC, March 1980.)

Ampicillin, a semisynthetic penicillin, was virtually 100 percent effective against the virulent human pathogen, salmonella, in 1967. Now, only one in four salmonella infections can be treated with ampicillin—previously the drug of choice for such infections. It is of interest that in 1967, less than 1 percent of salmonella strains exhibited concurrent resistance to six or more antibiotics; yet only 8 years later, that figure has increased to almost 10 percent. The rapidly changing resistance profile of salmonella is the subject of a recent center for disease control study which estimates that 30 percent of all clinically significant extraintestinal salmonella infections were inappropriately treated as a result of declining antibiotic effectiveness. (CDC, June 1980.)

Penicillin—once universally effective against gonorrhea, now exhibits in the target strains a strong penicillin resistance. In fact, cases of penicillin-resistant Niesseria gonorrhea increased 66 percent during the first 4 months of 1980 compared to the same period in 1979. (CDC, May 1980.)

Ampicillin—Once the drug of choice for treatment of Haemophilus influenza, the most common cause of bacterial memingitis in children and infants, is now virtually useless for such therapy and has been supplanted by other antibiotics with substantially greater toxicity and a lower margin of safety. (Pediatric News, 1979.)

E. coli—The most common cause of urinary tract infection in man are now exhibiting significant resistance to sulfonamides, generally the drug of choice for such infections. Moreover, resistant E. coli in the intestine of man also constitute a reservoir of organisms capable of transferring resistance to other intestinal pathogens. This presents perhaps the greatest hazard to human health arising from the use and misuse of antibiotics. (Federal Register, vol. 42, No. 168–Aug. 30, 1977, p. 43780.)

The list is merely illustrative and provides but a glimpse at overwhelming evidence which clearly demonstrates that once powerful antibiotics have been rendered virtually useless or severely compromised.

The element common to all of these situations is the presence of resistant-plasmids (R-plasmids) in the antibiotic resistant bacterial population. R-plasmids are genetic elements which carry transferable genes for drug resistance. They occur in both pathogenic and nonpathogenic bacteria alike. When exposed to an antibiotic, those bacteria which contain the appropriate R-plasmids survive, those which do not are inhibited.

This selective pressure of antibiotics is perpetuated and strengthened by continuous uses such as the practice of administering subtherapeutic levels of antibiotics in animal feeds, ostensibly for the purpose of growth promotion and diseases prevention. Of the utmost concern is the fact that the primary antibiotics used in this practice, penicillin and tetracycline, also have clinical significance for man. Furthermore, a full 50 percent of all antibiotics manufactured in this country are used for animal feeds.

Thus, an ideal situation now exists on the feedlot for the continuous selection and proliferation of bacteria which bear R-plasmids to penicillins and tetracyclines. Those resistant bacteria are then transferred to humans in a variety of ways where they may colonize and cause diseases for which only a compromised form of therapy exists.

The individual steps in this causal chain have been repeatedly documented, and attest to the bona fide nature of the health risks.

Furthermore, I believe it important that the subcommittee take a detailed look at the scientific basis for the concerns I have raised here. I am confident that such inquiry will only pursuade the doubtful and reinforce the persuaded. Toward that end, I call your attention to the following diagram of the causal chain.

Step 1	Step 2	Step 3	Step 4	Step 5
Antibiotics in feeds increase the prevalence of R+ bacteria in animals	Meat products contain R+ bacteria of animal origin.	R+ bacteria from animal sources can colonize man or pass R factors on to human flora.	Colonization usually precedes infection in man.	Infections due to R+ organisms are a significant clinical problem

Steps in the reasoning that antibiotics in animal feeds result in an increased incidence of human infections due to bacteria containing resistance factors (R+).

Source: Gardner, P., Journal of Infectious Diseases, vol., 138, No. 1, July, 1978, p. 102.

Step 1.—Antibiotics in feeds exert a strong and continuous pressure that favors the selection and proliferation of bacteria that are resistant to the antibiotics in the feeds (Antimicrobial Agents and Chemotherapy, December 1974).

Step 2.—Meat products contain drug resistant bacteria of animal origin in significant amounts (Nature, 1976).

Step 3—Drug resistant pathogenic and nonpathogenic bacteria of animal origin are transmitted to humans through direct contact with animals or agricultural products or through any number of indirect environmental pathways. These bacteria may then colonize the human host and cause disease for which only a compromised form of therapy exists, or they may pass on their resistance to organisms in the host flora, thereby creating a vast reservior of antibiotic resistant genes for subsequent transfer. This is perhaps the most controversial step in the causal chain, with critics maintaining the existence of biological barriers to the transfer of bacterial resistance between animals and humans. I ask that those critics reconcile their statements with the findings of Anderson (J. of Gen. Micro., 1975), Levy (Nature, 1976; J. Infectious Diseases, May 1978; New Engl. J. Med., 1976), Babcock (Applied Microbiology, 1973), Elwell (Infection and Immunity, August 1975; Antimicrobial Agents and Chemotherapy, March 1977), Siegel (Antimicro. Ag. Chem. November 1975), Falkow (testimony before Subcommittee on Oversight and Investigations, Committee on Interstate and Foreign Commerce, Antibiotics in Animal Feeds, Serial No. 95-68, Sept. 19, 23, 1977), and Novick (Annals of New York Academy of Sciences, In Press; Personal Communication, July 1980); This research has shown in clear and unequivocal fashion striking compatability of resistance mechanisms known as plasmids, from bacteria of animal and human origin. Furthermore, plasmids that once were found only in the enteric bacteria of animals and humans are now appearing in H. influenza and N. gonorrhea. From this evidence it can only be assumed that similar and identical plasmids have a common origin and are attributable to the sustained selective pressure of antibiotic usage.

Steps 4 and 5.—These links in the causal chain have been previously discussed and are elaborated in the references listed under step 3.

Perhaps the best short summary of our understanding of the causal chain is presented in the July 1979 Office of Technology Assessment Report entitled, "Drugs in Livestock Feed," p. 42:

> While the causal chain between food animals or their edible products and disease in humans may not be completely demonstrated in any given case, each step in the chain has been documented repeatedly. With the added criterion that the infectious agent in the animal or its edible product be shown to be caused by antibacterial supplements in the feed, the causal chain is even more difficult to prove in any specific case. Thus there is disagreement over the interpretation of any specific case but no real disagreement over the overall conclusion that food animals are the source of some infections in humans and that the use of antibacterials in feeds is one cause of the growing pool of drug-resistant pathogenic bacteria. Instead, the disagreement is over the exact risk from this enlarging pool and the contribution of antibacterials in animal feeds to the problem.

I will discuss the outstanding question of risk quantitation later in my testimony. I should point out to you at this time, however, that numerous well-documented case studies of plasmid-mediated transfer of drug resistance do exist from both clinical (Antimicrobial Ag. Chemo., April 1980) and agricultural experience (JAMA, February 1980; CDC, July 1977).

I have presented but a capsule summary of the pervasive role of R-plasmids in declining antibiotic efficacy. I have made available to you numerous articles which document this growing morass.

I ask unanimous consent that those be included at the conclusion of my statement. [See p. 17.]

Mr. **Waxman**. Without objection, those will be included in the record.

Mr. **Dingell**. A further danger lies in the fact that we are being lulled into a state of complacency by the belief that new antibiotics can readily be developed to replace the ones currently in decline. Indeed, the growing obsolescence of crucial therapeutic antibiotics has exerted increased pressure to develop substitutes. Unfortunately, a declining rate of discovery of new antibiotics strongly suggest that they are, like fossil fuels, an exhaustible and depletable resource. The proliferation of bacterial-resistance mechanisms not only has vastly increased the costs of innovation, but has forced the use of succeeding waves of expensively developed new antibiotics which account for most of the antibiotic dollar volume in this country.

These factors when viewed collectively, spell nothing but utter doom for the future efficacy of human antibiotics unless action is immediately undertaken to remove medically significant antibiotics from the feedlot, where the selective pressures are strongest.

I believe that the members of the subcommittee should also be aware of a number of specious and vapid objections that historically have been raised on this issue. First, it will be maintained that therapeutic uses have a more significant impact on bacterial resistance than subtherapeutic uses. The fact of the matter is that antibiotics exert a selective pressure wherever and whenever they are present in quantitities that exceed the no-effect level for a given antibiotic. Since both subtherapeutic and therapeutic use substantially exceed theoretical no-effect levels, the selective pressure is maintained regardless of absolute dose. I call your attention to the article by Rollins ("Antimicrobial Agents: Chemotherapy," May 1975). Second, the point will undoubtedly be raised that we do not see an increased incidence of certain diseases that might be expected to result from subtherapeutic uses. The point to keep in mind is that once disease does occur, therapy will be compromised regardless of the incidence rates, whether incidence rates increase, remain stable or decline.

It should be noted by one and all that we are not the first country to be faced with this menacing problem, but we unfortunately may be the last to put it to rest. Over the past 13 years, numerous studies and assessments of this contentious issue have been conducted. The Swann Commission in Britain (1969), the FDA task force (1972), the World Health Organization (1974, 1976, 1978), the FDA Antibiotics in Animal Feed Subcommittee (1975), the General Accounting Office (1977) and the Office of Technology Assessment (1979) all have conducted assessments of the known and potential hazards to humans and animal health resulting from the use of subtherapeutic doses of antibiotics in feed. I submit the 1976 and 1978 WHO reports for the subcommittee's review.

Without exception, restrictions on antibiotic use, particularly for penicillins and tetracyclines, were recommended. I would like to call your attention to pages 10 and 11 of the 1976 World Health Organization Report on this matter. It states:

> Man is incidently exposed to the acquisition of R-plasmids from enteric bacteria arising from the use of antibiotics in animal rearing and in medicine. The distribution of these bacteria is now so wide in the general environment that it is no longer necessary to attempt to relate their appearance in the individual to the use of the antibiotics concerned. It is their use in the community as a whole that is now the overriding influence, and it is only by applying communal measures that there can be any hope of rectifying the situation, though it has now advanced so far that it is debatable whether it can be repaired.

On page 11, you will find the following recommendation:

> Drugs that are therapeutically useful, actually or potentially, should be excluded from use as animal feed-additives.

A more ringing or meaningful endorsement of the intent of H.R. 7285 would be difficult to find.

The Office of Technology Assessment, the arm of Congress which analyzes technical and scientific issues for application to legislative debute, in its report Drugs in Livestock Feed, also called sober attention to the magnitude of present and future health risks of subtherapeutic uses, the potential irreversability of inaction and the ready availability of substitutes. OTA concluded that, "The health risks from the development of bacterial resistance to antibacterials in feed are of greater concern than the risks of cancer from DES and furazalidone as used livestock practices."

Let us now turn to another group of analyses which have attempted to enlighten us on this matter. In March 1980, the National Academy of Sciences (NAS) referred to by my good friend Dr. Carter, issued its report on antibiotics in feeds with conclusions that reflect upon the nature of the request: mission impossible. The Academy was asked, in essence, to produce the bodies of victims of subtherapeutic uses, and concluded that a comprehensive all-encompassing study to demonstrate this could not be realized or even approximated because of insurmountable technical difficulty. I note with some curiosity the NAS' exceedingly cautious tones and their inclusion of a yet to be released report by the Council for Agricultural Science and Technology (CAST). In light of the resignations of seven distinguished scientists en mass from the CAST panel on antibiotics in feeds due to coercive and deceptive attempts to bend science in a manner favorable to the pecuniary interests of the CAST membership, I question very strongly the National Academy's use of the CAST paper as a resource for its report. I submit for the subcommittee's direct attention a series of communications with CAST and the scientific panel that resigned in disgust from further participation in the CAST effort. I call particular attention to the letters of July 3, 1980, from Dr. Stanley Novick, which reiterate that the cause of the mass resignation was the collective and unanimous belief that further involvement with CAST would not only be futile from the standpoint of maintaining balance in the report, but also would constitute a compromise of professional credentials and integrity.

It is also worth note that the Academy's 1969 report on this very issue recommended restrictions on the use of antibiotics very similar to those contemplated by H.R. 7285, cosponsored by the chairman of this subcommittee and myself.

And last, we come to the research of the Animal Health Institute (AHI). That certainly is a name with a genuine ring to it. Furthermore, their brochure, "All About AHI," identifies them as the "unified voice of a responsible industry." In examining their membership, however, one finds no veterinary or related organizations, only the animal drug manufacturers. At this time, I would like to call your attention by Dr. Stewart B. Levy, in the New England Journal of Medicine which assesses the emergence and transfer of antibiotic-resistant bacteria in the environment as the result of subtherapeutic practices. I quote from that journal, page 588, volume 295, number 11, 1976:

> The rise in frequency of resistant organisms in our environment is the obvious result of antibiotic usage. The only means to curtail this trend is to control the indiscriminate use of these drugs. The present findings clearly demonstrate, however, that antibiotic-supplemented feed is a factor contributing to the selection of human-resistant strains of bacteria. These data speak strongly against the unqualified and unlimited use of drug feeds in animal husbandry and speak for re-evaluation of this form of widespread treatment of animals.

I point out to the subcommittee that Levy has published two additional articles—Nature, 1976; and J. of Infectious Diseases, May 1978—both of which contain identical recommendations and also were issued years ago. But these three distinguished pieces of research have more in common than their author and recommendations, for they were all funded and supported and summarily ignored by this very group that supposedly concerns itself with animal health, and later on this very afternoon, this same group will come before you and assert that all is right with the world regarding the use of antibiotics in feeds. I question whether AHI has any more concern for animal health than your local dog catcher, and suggest a prompt revision of their brochure. They will doggedly resist the reasonable proposal put forth in H.R. 7285 even when faced with evidence from their own research that confirms the soundness of its policy and intent. Such groups are always eager to use science as a schill, and seek comfort in and profit from uncertainties.

To gain an international perspective on the type of restrictions contemplated by H.R. 7285, I refer you to an article by Van Leeuwen, a most esteemed member of the European public health community—Antimicrobial Agents Chemotherapy, August 1979. His study documented a nationwide decline in the Netherlands or tetracycline-resistant salmonella which coincided with a ban on the use of tetracyclines in animal feeds. The British experience is detailed in the May 1980 article from the British Medical Journal.

During the course of this hearing, voices will be heard to cry out that the impacts are too severe, and that the farmer and consumer will lose. Nothing could be further from the truth. I call the subcommittee's attention to the testimony of Mr. Charles Hassebrook of the Center for Rural Affairs, Walthill, Nebr.

The Center for Rural Affairs is a spokesman for the small livestock raiser in the Midwest. Mr. Hassebrook's testimony speaks glowingly of the favorable impacts that restrictions on antibiotic use in feed would have on the small raiser, as it would impede the rapid trend toward concentration in the hog industry, which has been made possible by the use of antibiotic-supplemented feed. This point is reinforced by the results of a recent first-of-its-kind survey of 1,100 Missouri farmers conducted by the University of Missouri, Columbia, which is discussed in the statement of Mr. Bill Heffernan, and the accompanying press release.

When contrasted with the statement of the pork producers, it becomes readily apparent that the economic impacts are not really a question of how much, but who. But even that must be debated in light of the economic analysis presented by the USDA in its report entitled, "The Economic Effects of a Prohibition on the Use of Selected Animal Drugs." I quote from page 2 of the Executive Summary: "While the results of this study must be considered as merely suggestive, they do indicate that the economic system would generally be quite resilient to a more restrictive policy on animal drug use." Again, in this study as in every other assessment of the economic impact of penicillin and tetracycline restrictions, the mitigating effect of substitutes was not taken into account. Had this been done, the impacts of such restrictions would be virtually undetectable.

I would like to assure the subcommittee that substitutes for penicillins and tetracyclines do, indeed, exist and in ample numbers, as the 1980 Feed Additive Compendium, and the listing from the FDA draft environmental impact statement on this issue attests. Furthermore, I call particular attention to the two articles from Feedstuffs magazine by the owners of two feed associations. I quote Drs. Shull and Cardon of Arizona Feeds who state in their article that "Disease situations change from place to place, but one thing is clear: The need for antibiotics in feeds is not universal."

I trust that the foregoing has provided the subcommittee with a thorough reading of my position and concerns. It is my firm belief that science has taken us as far as it can on this issue.

We now have before us a policy issue not a simple one mind you, but a policy issue nevertheless, which calls upon us to answer a slightly different set of questions.

What is proof? At first blush, the call for proof seemingly appeals to an objective, infallible standard. We have seen that the type of study that would provide more conclusive evidence cannot even be approximated. We have viewed an expansive body of literature which documents every step of the causal chain leading to genuine and potentially irreversible health impact in humans.

Moreover what is our course when the proof is unattainable and its consequences unthinkable? In these circumstances, we actually come to rely on the predictive value of science to an ever greater extent. Of all the known instances where a body of scientists and health professionals and policymakers were faced with making a judgment on the matter before the subcommittee, the recommendation was to restrict or limit the use of essential antibiotics for subtherapeutic uses.

The other question which we must always ask ourselves as policymakers is, when is there enough data to justify action? When does the body of the evidence and expert judgment reach a point where further investigation proves to be of limited value and utility? This is decidedly a policy question which calls for prudent judgment. There will be those who continue to clamor for more research. They will say that there is not sufficient information to make a decision. They will say the science is not there. Well, let me just show you what information we do not have and what science is not there.

I have here two printouts.

By the way, I should introduce my two interns Joe Xuereb and Andy Halpern, who have assisted on this matter.

These two printouts, gentlemen, represent but a cursory search of the medical literature for just the last 5 years, yet it yielded in excess of 500 citations. Had I searched the files back to 1959, when plasmid-mediated resistance was first discovered, this printout would wrap around the Rayburn Building and then some. Yes, it is true that in this stack no study will be found which states that the use of antibiotics in animal feeds accounts for *x* percent excess morbidity and mortality in the United States—and I hope to hell there never will be such a study.

The time has come for us to stop giving credence to the utterances of troglodytes and at long last, recognize the underpinnings of truth.

Mr. Chairman, there are some thoughts that I think need to be borne in mind in consideration with H.R. 7285. H.R. 7285 deals most principally with the use of subtherapeutic dose of antibiotics in animal feed. It does not foreclose the use of those same antibiotics to cure animals which are diseased.

It is not something which would foreclose the use of other antibiotics or other growth agents which are not accompanied by the consequences that we would find from this subtherapeutic use, so considerable opportunity for drug manufacturers and for animal feed manufacturers to continued marketing feeds which might have the benefits which are alleged for current use of penicillin and tetracycline would continue to exist. It would remove from animal feeds penicillins, tetracyclines and a few other drugs which are of particular importance in curing major human diseases.

There are a couple of other thoughts with regard to these matters which are important. First of all, there is no real showing that these drugs are growth inducers. They might suppress disease and so be helpful, but that is of questionable value, with the supporting data for such claims having not been updated since the early sixties.

Equally important with this, Mr. Chairman, is the fact that powerful drugs like penicillins and tetracyclines have a number of effects inside the human body. The first is bacteria become more resistant to these particular drugs, large and larger doses are required.

The consequences are that many persons who might otherwise not cross the threshold of allergic and other reactions, which would be destructive to the human recipient of these drugs, might all of a sudden find themselves adversely affected by the larger required doses.

Now, I do applaud the efforts of industry to see to it that drugs are made available more broadly, and I recognize that these drugs are perhaps more broadly available to humans because they are made in part for animals, and that is I think a small and modest side benefit, but I don't believe that it weighs against bacteria which are able by reason of the wide use of these substances throughout the animal feed world in inducing not only strains of bacteria which in their own right are resistant to the drugs, but which are able to transmit across different species of bacteria the resistance to these drugs, something which is, I believe, a source of very real and potential peril to the people of this country and the rest of the world.

I can only tell you that if you wish to contemplate some consequence which would be extremely dangerous, contemplate, if you please, the situation where a person who might otherwise be cured might suffer a compromise in therapy by reason of inadequacy of the drug, by reason of the resistance or contemplate, if you will, a person who, because he might have to have a longer exposure to the drug, or a greater exposure in terms of the amount used, would suffer some kind of a toxin or allergic reaction which might either make him severely sick or might actually in fact kill him. I think you can see the consequences in individual cases, and it is not beyond the realm of possibility to extrapolate those into large-scale situations, which could severely afflict very large numbers of persons.

Last of all, Mr. Chairman, the thought that we might be in some way deficient on scientific research or literature search on this, I believe, has been abundantly laid to rest by the rather lengthy survey which I have produced to you, which has been put together over the last 5 years, indicating that there is strong need to bring these matters under control, and I would ask that, if there is room in the record, that last document be included therein also.

Mr. **Waxman**. Without objection, we will receive the printout and insert it in the record at the discretion of the chairman.

Mr. **Dingell**. I do thank you.

[Testimony resumes on p. 305.]

[The groups of articles referred to follow:]

CENTER FOR DISEASE CONTROL

MMWR

MORBIDITY AND MORTALITY WEEKLY REPORT

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International Notes

Multiply Antibiotic-Resistant O-Group 1 *Vibrio cholerae* — Bangladesh

For the past decade, a representative sample of O-group 1 *Vibrio cholerae* specimens collected from patients presenting to the Dacca Hospital and the Matlab Field Station of the International Center for Diarrheal Disease Research, Bangladesh (ICDDR,B), have been screened for antibiotic sensitivity. The observed pattern of uniform sensitivity changed little during that time. Recently, however, 5 of 28 (18%) isolates tested from the Matlab field area in a 6-week period were found to be resistant *in vitro* to tetracycline, ampicillin, kanamycin, streptomycin, and trimethoprim sulfamethoxazole. These vibrios belonged to the El Tor biotype; they included both Ogawa and Inaba serotypes and were El Tor phage-type 4, similar to current isolates in Bangladesh. The abrupt emergence of multiple drug resistance suggested that an R-plasmid was involved.

To confirm these observations, 167 additional vibrio specimens obtained from patients of the Matlab Field Station were tested. The earliest resistant strain was identified from a stock culture isolated from a patient at the beginning of the recent seasonal epidemic; 27 more multiply antibiotic-resistant vibrio (MARV) isolates were subsequently identified.* The percentage of isolates demonstrating resistance increased from 5%, in the first month of the epidemic, to 13%, 28%, 36%, and 15% for the next 4 months.

In retrospect, physicians at the Matlab Field Station had made clinical observations consistent with these *in vitro* resistance patterns. Some cholera patients, contrary to customary hospital course, continued to purge heavily after 2 days of hospitalization and 8 doses of tetracycline. Vibrios continued to be cultured from the stools of at least 2 patients treated with more than 12 doses of tetracycline. A retrospective examination of clinical records of resistant and nonresistant cholera cases indicated that while all cholera patients were indistinguishable at presentation, patients with MARVs purged for a longer period than those infected with sensitive strains.

Two cholera patients with the same antibiotic resistance pattern were identified at the Dacca Hospital. The first patient, a 25-year-old woman, arrived in Dacca from Matlab just before she became ill and was treated with oral therapy alone. The second patient, a 10-year-old boy, was traced to his home in Bajitpur, Mymensingh District, Bangladesh—70 kilometers northeast of Dacca. Neither patient had a history of travel outside of Bangladesh or of antibiotic use.

The plasmid coding for multiple antibiotic resistance has been transferred from one of the resistant vibrios to *Escherichia coli* $K\text{-}12F^{-}lac^{+}Nx^{r}$ receptor strain in the ICDDR,B laboratory. Further epidemiologic and microbiologic studies are in progress.

Editorial Note: The emergence of plasmid-borne, multiple antibiotic resistance in cholera has been documented previously from *in vitro* studies of O-group 1 *V. cholerae* and from occasional clinical isolates (*1,2*). The first outbreak, however, was only recently reported from Tanzania (*3*). The pattern of resistance in these vibrios was different from that

Vibrio cholerae – Continued

in Bangladesh but included tetracycline, the current drug of choice for cholera. While antibiotics are not essential to the treatment of the disease, they shorten the duration and volume of purging, the duration of excretion of vibrios, and the amount of fluid replacement required. Further *in vitro* studies and, perhaps, clinical trials will be needed to identify alternative antibiotics. The Bangladesh MARV is sensitive to furazolidone *in vitro*. Physicians, when treating cholera patients not responding to tetracycline, should consider antibiotic resistance. This can be confirmed by documenting continuing vibrio excretion (by dark field microscopy or stool culture) in patients given more than 8 doses of tetracycline, or by antibiotic susceptibility tests on the isolate. These patients will require more oral and/or intravenous therapy than other cholera patients. Adequate fluid and electrolyte replacement should be maintained until purging stops and fluid balance is re-established. It would also appear that the efficacy of tetracycline prophylaxis for *V. cholerae* has been compromised in this, and possibly other, cholera-endemic areas.

Although this outbreak was first identified in Matlab, an area under intense microbiological surveillance, the organism is probably more widely spread, an impression supported by the case from the Mymensingh District. The geographic distribution of this resistance pattern will not be known until antibiotic sensitivity testing of vibrios is performed in all countries.

Further investigations will be needed to predict whether this change in antibiotic sensitivity will be long-standing or reversible, and what its clinical consequences and public health importance will be.

Reported by MI Huq, ARMA Alim, and Dr LN Mutanda, Microbiology Br, Dr Md Yunus, Physician-in-Charge, Matlab Field Station, Dr MU Khan, Head, Disease Transmission Working Group, ICDDR,B.

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Change in Frequency of Drug Resistance of Salmonella Isolates Between 1967 and 1975

No. of drugs	Percentage of Resistant Isolates	
	1967(n=[illegible])	1975(n=754)
One or more	[illegible]	31.6
Two or more	[illegible]	[illegible]
Six or more	[illegible]	5.0

Findings based on human non-typhoid *Salmonella* isolates were sent to CDC from the 48 contiguous states. Only one strain from each known outbreak of salmonellosis was included, and duplicate isolates from the same patient were excluded. Statistically significant increases in frequencies of resistance were found for streptomycin, sulfonamides, ampicillin, kanamycin and chloramphenicol.

Based on *in vitro* considerations of susceptibility and questionnaire information concerning treatment, we estimate that [illegible] clinically significant extraintestinal infections in the 1975 [illegible] were given inappropriate treatment.

Source: Bacterial Disease Division, Center for [illegible]
June, 1980

CENTER FOR DISEASE CONTROL

MMWR

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Epidemiologic Notes and Reports

An Outbreak of Penicillinase-Producing *Neisseria gonorrhoeae* — Shreveport, Louisiana

From January 22-April 29, 1980, 28 cases of gonococcal infection caused by penicillinase-producing *Neisseria gonorrhoeae* (PPNG) were reported in Shreveport, Louisiana.

On January 21, an isolate of *N. gonorrhoeae* was confirmed as PPNG by the State Health Department Regional Laboratory, Shreveport (SHDRLS). This isolate was from a urethral culture obtained on January 15 from a 34-year-old man with gonococcal urethritis; this patient was first diagnosed on November 27, 1979. He received repeated treatment for persistent urethritis: ampicillin 3.5 g and probenecid 1 g p.o. (November 27), 4.8 million units of aqueous procaine penicillin G IM with probenecid 1 g p.o. (December 17) and tetracycline hydrochloride 500 mg 4 times daily for 7 days (January 15). On January 22, the patient was recultured, interviewed, and treated with spectinomycin 2 g IM. Cultures taken on January 22 and on February 4 were negative.

Two additional PPNG patients were identified among the sexual partners of the index patient, and intensive control measures were implemented. All patients were assigned top priority for interview and referral of their sexual partners. The SHDRLS began to screen all gonococcal isolates for penicillin resistance with disk tests; all resistant isolates were subsequently tested for beta-lactamase production. All positive PPNG findings were subsequently confirmed by the State Health Department Central Laboratory in New Orleans.

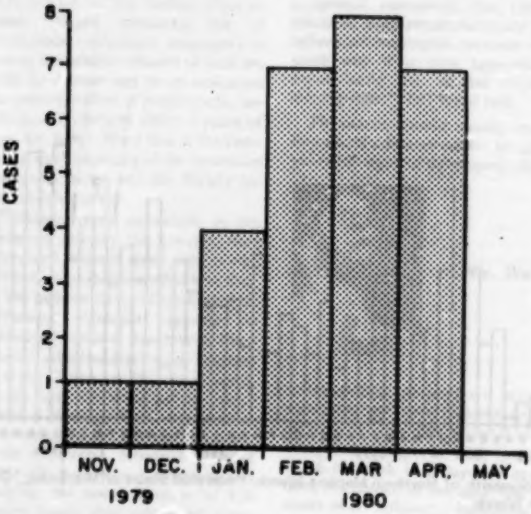
Figure 1 shows the occurrence of PPNG cases by the month in which individual patients first sought care. The average age of the 12 men was 25.7; the 16 women averaged 20.5 years of age. All patients resided within the Shreveport-Bossier metropolitan area. Of the 16 infected women, 2 had pelvic inflammatory disease (PID), one had suspected PID symptoms, and one had a Bartholin's gland abscess. The 28 patients were distributed in 8, apparently unrelated, chains of infection; no direct evidence of importation was obtained.

Screening approximately 400 gonococcal isolates for penicillinase production assisted in the early identification of 9 of the PPNG cases. Five patients (4 men and 1 woman) sought care in the Shreveport Venereal Disease Clinic because they had symptomatic disease. A total of 56 sexual partners, including 14 who were subsequently shown by culture to be infected with PPNG, were examined and treated. An additional 4 out-of-state contacts were examined, and 2 (1 PPNG, 1 non-PPNG) were found to be infected. The intervals between the patients' initial visits and identification and treatment of PPNG were shortened from an average of 2 weeks at the beginning of the outbreak to approximately 3 days when the outbreak stopped. No additional patients have been identified since April 29.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES / PUBLIC HEALTH SERVICE

Neisseria gonorrhoeae – Continued

FIGURE 1. Distribution of cases of PPNG, by month of first visit to Shreveport Venereal Disease Clinic, November 1, 1979-May 22, 1980



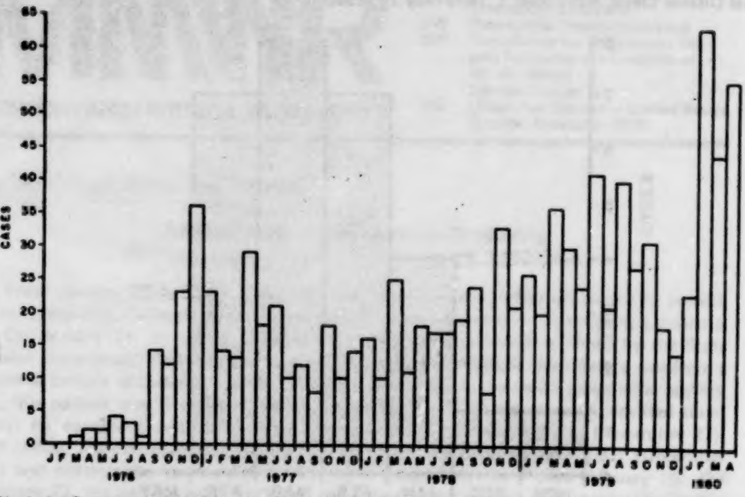
The Bureau of Laboratories, CDC, tested the antimicrobial susceptibility of 20 of the Shreveport PPNG isolates, including at least 1 isolate from each chain of infection. The pattern of susceptibility to 12 different antimicrobial agents was virtually identical for each isolate and very similar to that of PPNG isolates examined from the Far East. *Reported by C Caraway, DVM, State Epidemiologist, L Hightower, Louisiana State Dept of Health and Human Resources; H Bradford, PhD, Director, Louisiana State Laboratory; Bur of Laboratories, and Bur of State Services, CDC.*

Editorial Note: From March 1976, when the first PPNG isolate was identified, through April 1980, a total of 1,022 cases of PPNG in the United States were reported to CDC (Figure 2). Although the incidence of PPNG remains low, 186 cases were reported in the period January-April 1980, reflecting a 66.1% increase in cases compared to the same period in 1979. Given this increase and continued PPNG importation from abroad, some areas of the United States may experience sustained transmission of PPNG similar to the outbreak in Shreveport. Although epidemiologic investigation of the Shreveport outbreak could not link the chains of infection directly to military cases or importation from abroad, anecdotal and bacteriologic information suggests such importation.

Delays in identifying early cases of persistent infection contribute to PPNG transmission. CDC continues to stress the need for post-treatment cultures 3-7 days following therapy for all gonorrhea patients. Even patients who return after 7 days should be recultured, as treatment failure is still possible; all positive isolates should be tested for penicillinase production. Spectinomycin 2 g IM should be administered to all patients who continue to be infected. The use of spectinomycin, however, should be restricted to patients who fail primary therapy (with penicillin, tetracycline or ampicillin); spectinomycin is not recommended as primary therapy for gonococcal infection.

Neisseria gonorrhoeae — Continued

FIGURE 2. Cases of PPNG, by month, United States,* March 1976-April 1980



*Includes Commonwealth of Northern Mariana Islands, Federated States of Micronesia, Guam, Puerto Rico, and Virgin Islands.

Prophylactic Antibiotics Indicated for Young Contact in Hemophilus Influenzae Meningitis

International Medical News Service

ATLANTA — The finding of an almost 600-fold increased risk of *Hemophilus influenzae* meningitis in young household contacts of patients with the disease may be an indication for administration of prophylactic antibiotics to contacts under 6 years of age, Dr. Joel I. Ward said at the combined annual meeting of the American Pediatric Society and the Society for Pediatric Research.

Although most physicians in the audience accepted this concept, they expressed concern about determining the most appropriate antibiotic to use.

The high incidence of associated *H. influenzae* meningitis episodes in household contacts was revealed in a national collaborative study carried out at the Center for Disease Control, Atlanta, said Dr. Ward, of the CDC.

Similar findings were reported at the meeting by Dr. Robert S. Daum, of the Children's Hospital Medical Center, Boston. In a 1-month period following the hospitalization of 120 primary cases, four additional cases were observed in household contacts.

Dr. Daum said this secondary attack rate of 2.3% for children under 5 years of age is approximately 800 times greater than the endemic attack rate expected, and suggests the need for prophylactic therapy for household contacts.

In the collaborative study, done during an 18-month period beginning in January 1977, 1,403 index cases of *H. influenzae* meningitis were identified in the 20 states in which bacterial meningitis is a reportable disease. About 82% of the households in which the disease occurred were contacted to determine the incidence of associated cases developing within 30 days of the index case.

Ten secondary cases were identified in nine families. The median age of the affected household contact was 1.75 years, with a range of 2 months to 5 years.

The risk of *H. influenzae* meningitis was found to be 585 times greater than among age-adjusted groups in the general population. The secondary attack rates were 3.4% (4 of 119) among contacts under 1 year of age, 1.5% (4 of 259) among contacts 2-3 years old, and 0.1% (1 of 1,309) among contacts 4-5 years old; there were no secondary attacks in contacts age 6 and older.

Because of these findings, "there is a general consensus that rifampin could be used prophylactically in *H. influenzae* meningitis contacts in the same way it is now approved for prophylactic use against *Neisseria meningitidis*," Dr. Ward said.

Physicians should closely observe household contacts under the age of 6 years for signs of developing disease.

Dr. Ward

Antimicrobial prophylaxis may be warranted for these children and for children in a day-care center if an outbreak occurs there, he said.

An outbreak in a day-care center does not consist of one case, but two cases of *H. influenzae* meningitis occurring within 30 days of each other might be an indication that prophylactic rifampin should be given to the other children, Dr. Ward said in an interview after his presentation.

Physicians in the audience expressed confusion about the recommendation of rifampin when little is known about dosage, duration of treatment, and effectiveness.

Dr. Ward commented that many practitioners facing this problem want to know what to use. Ampicillin and a combination of trimethoprim and sulfamethoxazole have not been shown to be consistently beneficial, he said.

Many antimicrobials can cure the disease but do not eradicate the organism from the nasopharynx.

"Until further data are available to the contrary, I would suggest the use of rifampin," Dr. Ward said.

"I am only talking about prophylaxis for families with children under the age of 6 years in addition to the index case. This is a small and select population," Dr. Ward told this newspaper.

His associates in this study were Drs. David W. Fraser, Brian D. Plikaytis, and Larry Baraff.

Dr. Daum's associates in his study were Drs. M. P. Glode, J. Leclair, A. L. Smith, and D. A. Goldman.

Change Called for in Antibiotic Therapy for Otitis

By Annette Oestreicher
New York Bureau Chief

NEW YORK — The management of otitis media should be changed in view of studies that challenge traditional assumptions about the disorder, physicians said at a symposium on otitis media.

The most significant finding, now confirmed in at least two studies, is that *Hemophilus influenzae* is a cause of middle ear infections in children over the age of 5 years. This has significant implications for appropriate antibiotic selection because older children with-ear infections are usually given penicillin, which is ineffective against *H. influenzae*, said Dr. Charles D. Bluestone, professor and director of otolaryngology, Children's Hospital of Pittsburgh, and professor of otolaryngology, University of Pittsburgh School of Medicine.

The problem is compounded by the growing problem of *H. influenzae* resistance to ampicillin, the drug of first choice for the treatment of infection associated with *H. influenzae*, Dr. Bluestone noted.

The concern over the problem of otitis media stems from the extremely high incidence of the disease in the first 2 years of life and the possible association of the disease with later learning disabilities.

In a separate presentation, Dr. John D. Nelson, professor of pediatrics, the University of Texas Health Science Center, Dallas, reported that otitis media accounted for 56% of 7,125 "sick-child" visits to Dallas pediatricians in private practice during a 7-month period.

In another presentation, Dr. Jerome O. Klein, professor of pediatrics Boston University School of Medicine, reported that a prospective study of 2,500 children in the greater Boston area followed for up to 4 years revealed that 34% had three or more episodes of middle ear infection in the first 2 years of life and that some of these children had 6-12 such episodes.

An additional 40% of children had one or two episodes of otitis media during the first 2 years of their life.

An "insidious and unrealized complication" is that fluid often remains in the ear after a complete course of antibiotic therapy and is not detected by the physician or the parents, Dr. Nelson said.

An analysis by Dr. Klein of 3,000 cases of otitis media reported in the literature revealed a 33% incidence of pneumococci associated with acute otitis media and a 20% incidence of nonencapsulated *H. influenzae* in children of all ages.

Dr. Nelson emphasized that "bacteria do not cause otitis media; they are associated with otitis media. The disease is caused by a malfunction of the eustachian tube that allows bacteria in the nasopharynx to enter the middle ear."

The studies showing a significant association of *H. influenzae* with episodes of otitis media in school-age children are disturbing because of the current practice of prescribing penicillin G or penicillin V automatically for older children. Penicillin is not an effective antibiotic against these bacteria, Dr. Nelson said.

"We have mistrained physicians by originally telling them not to worry about *H. influenzae* in children over the age of 4 years," he said.

The three physicians expressed concern about the 15% incidence of ampicillin-resistant *H. influenzae* isolates. Given a 20% incidence of *H. influenzae* in middle ear isolates and a 15% incidence of ampicillin-resistant strains, approximately three percent of all episodes of otitis media will be unresponsive to this treatment, they noted.

For the last 2-3 years, Dr. Nelson has been recommending the use of penicillin and a sulfa drug, or preferably, erythromycin and a sulfa drug, for patients with otitis media.

The lack of a fixed combination of these antibiotics involves problems with compliance and possibilities for dosage error by the parents, however, he said.

Drs. Klein and Bluestone said they still prescribe ampicillin as the drug of first choice in the treatment of otitis media but warn that resistance to treatment should be closely watched for.

Dr. Nelson believes the approval of trimethoprim and sulfamethoxazole for the treatment of otitis media associated with resistant *H. influenzae* was premature because the data are sparse, but Dr. Klein said his experience with the combination has been positive.

Strains Only Inhibited

A cephalosporin, Cefaclor, will be available soon and has been shown to be active against almost all strains of *H. influenzae* and pneumococci, Dr. Nelson said.

A "disturbing fact" is the demonstration that some bacterial strains are inhibited but not killed by antibiotic therapy. The carrier state will not be eliminated if *H. influenzae* are merely inhibited, Dr. Nelson said.

Attempts to prevent otitis media by the prophylactic administration of an antihistamine-decongestant combination have not been successful. The use of a decongestant to hasten the resolution of the disease or the duration of fluid present in the middle ear was also not effective, he said.

These studies indicate that decongestants have no place in preventing recurrences or improving resolution time, Dr. Nelson commented.

Dr. Klein said antibiotic chemoprophylaxis has been used with some success to prevent acute recurrences, but "we are concerned that the fluid may persist and not be detected and that the side effects of prolonged use of antimicrobials are not known."

Dr. Nelson said it does not seem reasonable that chemoprophylaxis should prevent the disease because "we believe that the bacteria do not actually cause the disease." Original results showing a benefit from this therapy have not been duplicated.

Dr. Klein said the use of a pneumococcal vaccine may be beneficial and is currently being tested in a double-blind study conducted by the National Institutes of Health, Bethesda, Md.

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Continuous Non-Therapeutic Use of Antibacterial Drugs in Feed and Drug Resistance of the Gram-Negative Enteric Florae of Food-Producing Animals

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Fecal samples from Illinois farm animals and Montana range cattle were examined for the frequency of gram-negative enteric organisms resistant to oxytetracycline, dihydrostreptomycin, or ampicillin. The Illinois farm animals were continually fed rations containing various antibacterial drugs. The Montana range cattle had minimal exposure to antibacterial drugs. The majority of samples from Illinois farm animals demonstrated 10% or more antibiotic-resistant organisms. In contrast, resistant organisms could not be detected in the majority of samples from Montana range cattle. The majority of *Escherichia coli* isolated from Illinois farm animals was resistant to various antibacterial drugs, whereas less than 1.6% of the isolates from Montana range cattle were resistant to any one of the antibacterial drugs tested.

A number of antibacterial drugs are routinely included on a continuous basis in the feed of animals used for the production of food. These drugs, most of which are also utilized in human medicine, are added to animal feed for therapeutic, prophylactic, and various production purposes. The agricultural applications of medically important drugs have been questioned because of the direct selective effects of the drugs favoring an increased occurrence of drug resistance in pathogens of animal origin. Furthermore, because of the transmissibility of resistance in gram-negative enteric organisms, resistant enteric organisms normally considered nonpathogenic may provide a reservoir of resistance for both human and animal pathogens.

Reports have documented the prevalence of resistance among specific members of the *Enterobacteriaceae* obtained from farm animals fed various antibacterial drugs (3, 5, 7, 8, 10-15). However, we have quantitatively examined the entire gram-negative enteric flora of fecal specimens, as well as *Escherichia coli*, to determine total proportions of antibiotic-resistant organisms. Farm animals continuously fed antibacterial drugs are compared to animals having minimal or no exposure to antibacterial agents. The results presented suggest the magnitude of the effect which the agricultural use of antibacterial drugs has had in favoring a predominately drug-resistant enteric flora in the farm animal.

MATERIALS AND METHODS

Media. MacConkey agar (Difco) was used for the determination of proportions of antibiotic-resistant, gram-negative enteric organisms in fecal samples. EMB agar (Difco) was used for secondary isolation of strains selected from MacConkey agar plates spread with fecal suspensions. Mueller-Hinton agar (BBL) was used for antibacterial drug-susceptibility testing. Dilutions of fecal specimens were made in sterile saline (0.85% NaCl).

Antibiotics. The following concentrations of antibacterial drugs in MacConkey agar were used: oxytetracycline, 20 μg/ml (kindly supplied by Pfizer, Inc.); dihydrostreptomycin, 25 μg/ml (also supplied by Pfizer, Inc.); and ampicillin, 50 μg/ml. Concentrations of oxytetracycline, dihydrostreptomycin, and ampicillin in agar were selected to provide the best possible correlations between Kirby-Bauer disk-susceptibility tests and the appropriate presence or absence of growth on agar.

Fecal samples. Fecal samples were collected from Montana range cattle using Culturette swabs (Medi/Flex Division, Medical Supply Co.). Other specimens were collected by placing approximately 20 g of feces in 50 ml of sterile (pH 7.2) buffered-glycerol-saline solution consisting of 4.2 g of NaCl, 4.03 g of $K_2PO_4 \cdot 3H_2O$, 1.0 g of KH_2PO_4, 300 ml of glycerol, and 700 ml of deionized water.

Method for quantitation of total and antimicrobial drug-resistant, gram-negative enteric organisms. Feces collected with Culturette swabs were suspended in 2-ml volumes of sterile saline.

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Relatively homogeneous suspensions of fecal samples in buffered-glycerol-saline solution were obtained by maceration of the sample with a small sterile stainless-steel spatula. All samples remained at room temperature for approximately one-half hour with occasional vigorous shaking. Debris settled out and the relatively homogeneous supernatant layer was used for dilution and plating. Duplicate 0.1-ml portions of serial 10-fold dilutions in saline were plated on MacConkey agar to determine the total numbers of gram-negative enteric organisms. Identical portions of each dilution were plated on MacConkey agar containing separately oxytetracycline, dihydrostreptomycin, or ampicillin. Plates were incubated overnight at 37 C. The number of organisms, resistant and sensitive, present in the undiluted suspension of each sample was calculated from an average of the number of colonies growing on MacConkey agar plates without antibiotic. Determination of concentrations of organisms resistant to oxytetracycline, dihydrostreptomycin, or ampicillin was based upon the numbers of colonies growing on MacConkey agar containing each antibiotic.

Isolation and identification of E. coli isolates. Lactose fermenting colonies were selected from antibiotic-free MacConkey agar plates and streaked on EMB agar. A single colony from the EMB plate was used to inoculate various biochemical tests and a nutrient agar (Difco) slant. Inocula of broth cultures for antibiotic-susceptibility testing were obtained from the nutrient agar slant. Organisms were identified according to the procedures of Edwards and Ewing (4).

Antibacterial drug-susceptibility testing. Antibacterial drug-susceptibility testing was performed as described by Bauer et al. (1). Isolates with intermediate resistance were considered susceptible for the purposes of this investigation.

RESULTS

Antibacterial drugs used on farms. All Illinois swine, beef cattle and calf, and poultry farms in this study routinely used feed containing antibacterial drugs. The antibacterial agents used as feed supplements are presented in Table 1. The information for this table was obtained from farm records and/or analysis of feed samples with high-voltage agar gel electrophoresis (9). Complete records of the antibacterial drugs and concentrations used were not always available and feed samples were not always examined by agar gel electrophoresis. Tetracyclines were the most commonly used agents, followed by penicillin and sulfonamides. Tetracyclines and penicillin were used in concentrations from 50 to 100 g per ton. Sulfonamides were utilized almost exclusively at 100 g per ton. Many of the farms periodically changed the antibacterial drugs used. One swine farm changed the antibacterial drug(s) used in feed every month. The monthly drug combinations used on this farm were: chortetracycline, penicillin, and sulfamethazine; tylosin; neomycin, and chlortetracycline; tylosin and sulfamethazine; penicillin and streptomycin; and finally furazolidone. It was not possible to detail the occasional parenteral or enteral therapeutic use of drugs.

TABLE 1. *Antibacterial drugs used continuously in feeds of Illinois swine, poultry, and beef cattle and calves*

Antibacterial drugs	Percent of farms using each antibacterial drug		
	Swine	Poultry	Beef cattle and calves
Tetracyclines	76	100	80
Penicillin	52	50	0
Sulfonamides	68	50	20
Streptomycin	20	0	0
Neomycin	16	50	40
Tylosin	16	0	0
Furazolidone	8	0*	0
No. of farms	25	2	5

Percentage of antibiotic-resistant, gram-negative enteric organisms in fecal samples from Illinois food-producing animals maintained on antibacterial drug-supplemented feeds. The proportions of antibiotic resistant to total organisms in fecal specimens from Illinois swine are presented in Fig. 1. Individual fecal samples (133) were collected from 30 different farms. The results are presented as a distribution of the samples according to ranges of percentage of resistant organisms.

Ninety-five percent of the swine samples

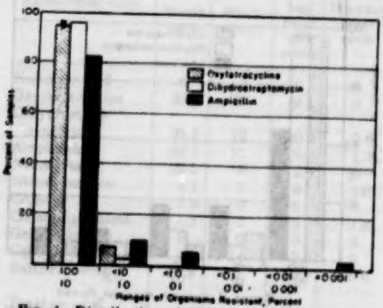

FIG. 1. *Distribution of Illinois swine samples according to percentages of antibiotic-resistant organisms.*

examined contained between 10 and 100% oxytetracycline-resistant organisms. Ninety-six percent of the samples demonstrated 10 to 100% dihydrostreptomycin-resistant organisms, whereas 82% of the samples fell into the same percentage range of ampicillin-resistant organisms. Very few of the Illinois swine samples contained less than 10% antibiotic-resistant organisms. Although not shown in Fig. 1, 77% of the samples were composed completely (100%) of oxytetracycline-resistant organisms. One-hundred percent dihydrostreptomycin-resistant organisms occurred in 73% of the samples, and 100% ampicillin-resistant organisms occurred in 29% of the samples.

Figure 2 presents the results of quantitating fecal samples from Illinois beef cattle and calves from 22 individual animals on seven Illinois farms. The proportions of samples containing 10% or greater antibiotic-resistant organisms were lower than those obtained with Illinois swine samples. Seventy-seven percent of the Illinois beef cattle samples contained from 10 to 100% oxytetracycline- or dihydrostreptomycin-resistant organisms. Forty-five percent of the samples were in the 10 to 100% range of ampicillin-resistant organisms. Sixty-two percent of the samples were composed completely of oxytetracycline- or dihydrostreptomycin-resistant organisms. Thirty-one percent of the samples were completely composed of ampicillin-resistant organisms.

The results obtained from quantitating proportions of resistant organisms in 18 composite poultry samples from 10 Illinois farms are presented in Fig. 3. Again, high proportions of the samples examined were composed largely of antibiotic-resistant organisms. Ninety-four percent of the samples had between 10 and 100% oxytetracycline-resistant organisms. Eighty-two percent of the samples contained 10% or greater dihydrostreptomycin-resistant organisms. Forty-one percent of the poultry samples fell into the 10 to 100% range of ampicillin-resistant organisms. One-hundred percent oxytetracycline-resistant organisms occurred in 37% of the poultry samples. Forty-one percent of the samples contained 100% dihydrostreptomycin-resistant organisms, whereas 6% of the poultry samples contained 100% ampicillin-resistant organisms.

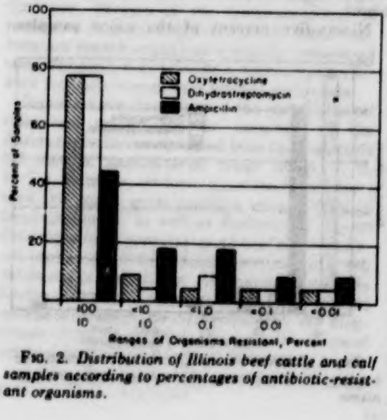

FIG. 2. *Distribution of Illinois beef cattle and calf samples according to percentages of antibiotic-resistant organisms.*

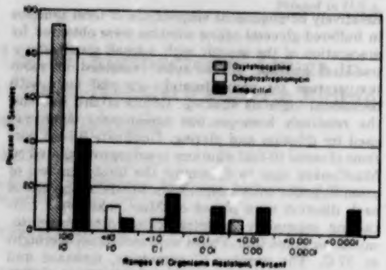

FIG. 3. *Distribution of Illinois poultry samples according to percentages of antibiotic-resistant organisms.*

Percentage of antibiotic-resistant gram-negative enteric organisms in fecal samples from Montana range cattle. Individual fecal samples (72) from Montana range cattle were examined for proportions of antibiotic-resistant organisms. The distribution of these samples according to ranges of percent antibiotic-resistant organisms is presented in Fig. 4. Only one (1.4%) of the samples contained greater than 0.1% oxytetracycline-resistant organisms. Two (3%) of the samples contained approximately 0.1% dihydrostreptomycin-resistant organisms. One of the 72 samples had 1% and four of the samples had 0.1% ampicillin-resistant organisms. Out of 25 ampicillin-resistant organisms from these samples, 22 were of the genus *Enterobacter*.

The initial suspension of feces from range cattle was considerably more dilute than the initial suspension of feces from previous groups of animals. As a result, fewer organisms were plated and the percentage ranges of antibiotic-resistant organisms could not be extended to the same low percentage ranges used in the previous figures. The bars of the last two

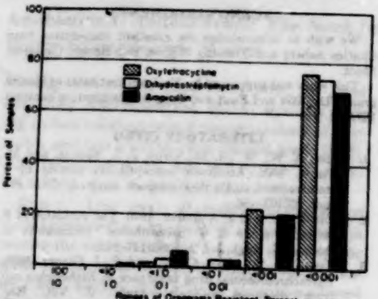

FIG. 4. *Distribution of Montana range cattle samples according to percentages of antibiotic-resistant organisms.*

percentage ranges of resistant organisms, i.e., ≤0.01 and ≤0.001%, represent samples in which resistant organisms were not detected. The samples with undetectable numbers of resistant organisms were assigned to either the ≤0.01 or ≤0.001% ranges according to the total number of organisms plated. It is apparent that resistant organisms were not detected in the great majority of the samples examined from range cattle.

Total antimicrobial drug resistances in *E. coli* from domestic animals with and without exposure to antibacterial drugs. Randomly selected *E. coli* isolates from all samples were tested for their susceptibility to various antibacterial drugs. Table 2 presents the percentages of *E. coli* isolates from each animal category resistant to each of the antibacterial drugs tested. With few exceptions, *E. coli* isolates from swine were more frequently resistant than *E. coli* from any other animal groups studied. Resistance to nalidixic acid and gentamicin did not appear in isolates from any of the groups. Approximately 90% of the isolates from swine and approximately half of the isolates from beef cattle and calves were resistant to oxytetracycline and dihydrostreptomycin. The difference between the percentages of isolates from poultry resistant to oxytetracycline (59% resistant) and dihydrostreptomycin (72% resistant) may be related to the small number of isolates examined, although quantitations of samples from poultry also revealed a degree of disparity in the proportions of organisms resistant to oxytetracycline and dihydrostreptomycin not seen in the quantitative results from swine and beef cattle and calves. Approximately 20% of the isolates from swine and 12% of the isolates from beef cattle and calves were resistant to neomycin. Resistance to nitrofurantoin, colistin, chloramphenicol, and cephalothin was uniformly low.

The occurrence of resistance in *E. coli* from Montana range cattle was minimal. None of the 431 isolates tested were resistant to nalidixic acid, oxytetracycline, neomycin, colistin, gentamicin, or cephalothin. A few of the isolates, from three to six of the 431, were resistant to dihydrostreptomycin, ampicillin, nitrofurantoin, chloramphenicol, or sulfamethazine.

All isolates resistant to oxytetracycline, dihydrostreptomycin, ampicillin, neomycin, chloramphenicol, and cephalothin were examined for the transmissibility of their resistance markers. Between 40 and 60% of the resistance from Illinois farm animals was transmissible. We were unable to detect transmissibility of any marker by the *E. coli* from Montana range cattle (unpublished data).

DISCUSSION

The results reported from samples of Montana range cattle are analogous in some respects to published reports of studies of humans living in primitive areas (2, 6). Like the subjects of these human studies, the range cattle had minimal or no exposure to antibacterial drugs. The lack of exposure of these animals to anti-

TABLE 2. *Total antimicrobial drug resistances of E. coli from Illinois swine, poultry, beef cattle and calves, and Montana range cattle*

Antibacterial drugs	Percentage resistant			
	Illinois swine	Illinois poultry	Illinois beef cattle and calves	Montana range cattle
Nalidixic acid	0	0	0	0
Oxytetracycline	89.8	59	49.1	0
Dihydrostreptomycin	93.2	72	50.0	0.6
Ampicillin	52.5	17	13.2	1.3
Neomycin	20.5	0	12.3	[illegible]
Nitrofurantoin	4.1	7	0	1.6
Colistin	0.9	0	0	0
Chloramphenicol	1.7	3	0	1.6
Gentamicin	0	0	0	0
Cephalothin	4.0	14	3.8	0
Sulfamerazine	82.9	21	29.2	0.6
Total no. of *E. coli*	530	29	106	431

bacterial drugs was reflected in the absence of oxytetracycline-, dihydrostreptomycin-, and ampicillin-resistant organisms in the majority of the quantitatively examined samples and the uniformly low prevalence of resistance found in *E. coli*.

In contrast, the extensive management and veterinary uses of antibacterial drugs on Illinois farms is correlated with a predominance of resistant enteric organisms. The proportions of resistant gram-negative enteric organisms and the incidence of resistance in *E. coli* isolates were highest for samples from Illinois swine. The high incidence of resistance in swine is probably related to the more extensive use of antibacterial agents in swine management to control animal disease.

Assessment of the potential hazard to animal or human health posed by a predominately resistant enteric flora of the farm animal could be, in part, based upon the magnitude of difference in the prevalence of resistance in florae of animals with and without continuous exposure to antibacterial drugs. The low prevalence of resistance reported for unexposed florae of the Montana range cattle may approximate the incidence of resistant organisms in the enteric florae of farm animals prior to the widespread agricultural use of antibacterial drugs. The continuous nontherapeutic use of these important drugs has been responsible for a substantial increase in resistant organisms of the farm animal. Because of the transmissibility of the genetic material mediating drug resistance (R factors) in gram-negative enteric organisms, it appears reasonable to assume that the increase in the proportions of resistant organisms in the farm animal has increased the opportunity for ecologically associated, pathogenic, gram-negative enteric organisms to acquire R factors. In addition, if food originating from the farm acts as a vector of organisms (or R factors), which may become resident in the flora of the consumer, the continuous use of antibacterial drugs on the farm may also be responsible for the formation of a reservoir of transmissible resistance in the consumer. Although animal-derived food is well recognized as a source of human salmonellosis, it remains to be conclusively demonstrated that organisms such as *E. coli* (or R factors) from the farm contribute to the composition of the flora of the consumer.

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Antibiotics in Animal Feeds: The Need for Better Epidemiologic Studies

Having debated the issue since 1970, the Food and Drug Administration (FDA) again is moving to ban subtherapeutic concentrations of penicillin and tetracycline from animal feeds [1, 2]. The reasoning which has led to the proposed FDA action goes roughly as follows (figure 1).

Step 1. Low levels of antibiotics in animal feeds promote the emergence of resistant bacteria among the normal flora of animals ingesting the feeds [3, 4]. Most interest is focused on the enteric flora and the high rate of plasmid-mediated (R factor) resistance among Enterobacteriaceae in the fecal flora of animals receiving antibiotics in their feed.

Step 2. Meat prepared for human consumption contains large numbers of enteric bacteria of animal origin [5, 6]. These organisms commonly harbor R factors.

Step 3. Bacteria of animal origin, when ingested by humans, may either colonize or pass on R-factor-mediated antibiotic resistance to organisms in the host flora [7–10].

Step 4. In humans, infection is commonly preceded by colonization with the infecting organisms [11].

Step 5. In human infections the outcome of therapy may be adversely affected if the organism is resistant to the prescribed antibiotic [12, 13]. Therefore, factors that promote resistance among bacteria pathogenic for humans constitute a health hazard.

An additional concern of the FDA is that the subtherapeutic use of antibiotics in animal feed may result in residues of antibiotics in tissue which will exert a selective force favoring the emergence of resistant bacteria in the flora of meat consumers. Related issues, which come mainly under the jurisdiction of occupational and environmental health agencies, include (*1*) the question of increased risk to workers in the meat production industry as a result of exposure to antibiotics or to bacteria and (*2*) the question of environmental risk due to the contamination of water and soil by runoff from feed lots where antibiotic-containing feeds are used.

Neither the opponents nor the proponents of the FDA ban have any serious disagreement regarding the first two or last two steps in the argument. The fiercest defender of the use of antibiotic additives in feeds will cheerfully admit that the practice alters the enteric flora of animals toward resistance and that these bacteria show up in meat products on grocery shelves, their numbers enhanced by the multiplier effect of food processing and the addition of other enteric bacteria resulting from food handling.

Likewise, there is little argument that in human infections colonization commonly precedes infection and that antibiotic resistance among enteric pathogens poses a significant limitation on our current armamentarium of antibiotics.

The battle lines are drawn at step 3 around the issue of whether bacteria from animals consumed as food colonize humans or pass R-factor-mediated antibiotic resistance to organisms in the host flora. Supporters of the ban on antibiotics in animal feeds cite evidence showing that (*1*) *Escherichia coli* isolated from animals can colonize the human intestine (although usually only transiently) when ingested in large amounts [7, 8]; (*2*) an increased prevalence of resistant organisms is found among workers handling antibiotic feeds and animals [14–16]; (*3*) the common *E. coli* serotypes of livestock and humans are more similar than previously recognized [17, 18]; (*4*) the R-factor patterns of resistant *E. coli* from animals and resistant *E. coli* from humans are often similar [19]; and (*5*) ani-

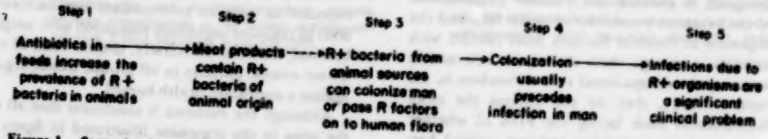
Step 1
Antibiotics in feeds increase the prevalence of R+ bacteria in animals
Step 2
Meat products contain R+ bacteria of animal origin
Step 3
R+ bacteria from animal sources can colonize man or pass R factors on to human flora
Step 4
Colonization usually precedes infection in man
Step 5
Infections due to R+ organisms are a significant clinical problem

Figure 1. Steps in the reasoning that antibiotics in animal feeds result in an increased incidence of human infections due to bacteria containing resistance factors (R+).

mals raised in the meat industry are an important reservoir of *Salmonella* [20]. Therefore, increased levels of antibiotic resistance in salmonella isolates from animals represent a human health concern.

Opponents of the ban feel that most animal bacteria are such poor colonizers of humans that they are part of a separate ecosystem. If this is the case, the increase in R-factor plasmids among enteric bacteria in animals is not likely to be of major significance to humans. Opponents of the ban contend that resistant organisms of animal origin are of small importance compared to the selective pressure created by the massive use of antibiotics in medical practice and the resultant problems of resistance among bacteria that are better colonizers of humans. In regard to *Salmonella*, the traditional epidemiologic emphasis on the importance of animal reservoirs has been challenged by (*1*) the observation that the susceptibility patterns of human salmonella isolates commonly differ from patterns of antibiotic resistance of salmonella isolates from animals [21] and (*2*) epidemiologic observations suggesting that human-to-human transmission may be more important than previously acknowledged [22]. Surprisingly, subtherapeutic levels of antibiotics in animal feeds do not appear to increase (and in some studies may reduce) the overall prevalence of *Salmonella* in chickens, cattle, and swine, although the percentage of antibiotic-resistant salmonella isolates is increased [2].

The argument has moved beyond debate of the phenomena. Almost everyone agrees that each step in the chain can occur under appropriate conditions. The question is, at what frequency does animal-to-human transfer of bacteria and/or R factors occur under normal circumstances? Existing epidemiologic studies have focused on whether farm families in direct contact with animals receiving antibiotics in feed show increased colonization with resistant organisms. These studies have yielded conflicting results and are difficult to interpret since they have not been designed to evaluate the relative contributions of the exposure to antibiotics in the feed and the exposure to resistant bacteria from contact with animals. Although these studies are relevant in assessing the occupational risks of workers in the meat industry, they do not address the more fundamental issue facing the FDA of whether meat products containing resistant animal bacteria constitute a health hazard. Two types of prevalence studies ought to shed significant light on these issues.

(*1*) *Studies of vegetarians and nonvegetarians.* If resistant bacteria of animal origin constitute a health hazard, strict vegetarians should have fewer resistant enteric bacteria when compared with a group of meat eaters. A negative result would indicate that dietary sources of animal bacteria and R factors are not significant determinants of human flora. In addition, a negative result also would indicate that the current levels of antibiotic residue in meat products do not create an ecologic pressure favoring emergence of resistant bacteria. A positive result would allow the opposite conclusions. One poorly controlled study of R-factor prevalence among vegetarians and nonvegetarians purported to show no difference but must be considered inconclusive [23]. The groups must be carefully controlled for factors such as socioeconomic status, family size, age of children, and antibiotic usage. A group of Seventh Day Adventists and neighborhood controls would constitute one acceptable study population.

(*2*) *Studies of abattoir workers, their families, and neighborhood controls.* Abattoir workers have heavy exposure to animal bacteria but are not exposed to the antibiotic-containing feeds. Abattoir workers therefore are exposed to the resistant organisms but not to the selective antibiotic pressure. As such they represent a good group for evaluation of the propensity of animal bacteria to colonize humans and for study of the secondary spread of animal bacteria and/or R factors via contact spread to family members. Determination of the prevalence of resistant enteric bacteria among abattoir workers, their family members, and neighborhood controls matched for socioeconomic status, family size, antibiotic ingestion, and other factors should yield information regarding the propensity of animal bacteria (and/or R factors) to colonize and propagate in humans. If significant colonization occurs, abattoir workers would be expected to have the highest prevalence of resistant organisms. If secondary spread occurs, family members would be expected to have an intermediate but increased level of resistant organisms compared with neighborhood controls. Conversely, similar rates of resistant enteric bacteria in all groups would argue against a significant health hazard.

Although the evidence is conclusive that all of the steps in the argument illustrated in figure 1 can occur, data bearing on whether, under normal circumstances, meat products contribute sigificantly to our burden of resistant bacteria remain indirect and inconclusive. The relative contribution of this source of resistant bacteria to other well-recognized factors such as overuse of antibiotics in medical practice and the inability to prevent effectively colonization of patients by resistant organisms in hospitals, remains to be determined. These are epidemiologic questions which can and should be answered by adequate epidemiologic studies which should benefit the FDA in reaching an enlightened decision regarding these economically important matters.

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Spread of antibiotic-resistant plasmids from chicken to chicken and from chicken to man

THE natural ecology of *Escherichia coli* and its infectious plasmids is not understood, although there is suggestive evidence that animals may serve as reservoirs for *E. coli* found in humans[1,2]. Investigation in this area becomes additionally important in view of the practice of introducing plasmids with pieces of foreign DNA into *E. coli*[3,4]. During an examination of the effects of antibiotic-supplemented animal feed on flora of farm animals and human personnel (ref. 5 and S.B.L., G.B.F. and A.B.M., unpublished), a study was initiated to determine if *R* plasmids and their *E. coli* hosts were naturally transferred among chickens and from chickens to human handlers. Our results illustrate the spread of antibiotic-resistant organisms from chicken to chicken and from chicken to man.

We used a temperature-sensitive chloramphenicol-resistance gene as a marker to identify a particular plasmid. *Escherichia coli* D1–7 (ref. 6), carrying *R222*, was treated with nitrosoguanidine[7] and a mutant expressing temperature sensitivity to chloramphenicol was selected from the surviving bacteria. The temperature-sensitive chloramphenicol-resistance property was easily transferred to other hosts. This finding indicated its presence on a plasmid. This mutant plasmid, designated *pSL222–6*, expressed resistance to chloramphenicol, tetracycline, sulphonamides and streptomycin at 32 °C, but at 42 °C did not express chloramphenicol resistance. *pSL222–6* was transferred by conjugation into two morphologically distinct *E. coli* isolated from chickens. An inoculum containing a mixture of the two recombinant bacteria was introduced directly into the intestines of four chickens by means of a tube placed in the cloaca. The chickens were caged separately and fed tetracycline-supplemented feed (Pfizer; tet-feed) to enhance colonisation with this tetracycline-resistant *E. coli*.

A repeat inoculation was carried out 4 d later although subsequent analysis showed that already at this time all of the faecal *E. coli* isolated from these chickens were resistant to chloramphenicol at 32 but not at 42 °C. Two chickens were then placed in two cages each containing 50 chickens. One cage (A) was placed on the tetracycline-supplemented feed; the other (cage C) was not. Two other cages containing chickens with (B) and without tet-feed (D) were also maintained in the barn at about 50 feet from the experimental cages. In this way, the effect of tet-feed on the spread of the marked plasmid from inoculated chickens to other chickens could be evaluated.

Table 1 Number of chickens excreting *E. coli* containing *pSL222–6**

Day	Cage A	Cage B	Cage C	Cage D
0	0	0	0	0
7	1	4	0	0
14	1	6	0	0
49	5	8	0	0
56	6	8	0	0
63	7	12	0	0
% Chickens excreting mutant *R* plasmid	14	24	0	0

*Does not include inoculated chickens placed in cages A and C; chickens in cages A and B were fed tet-feed; C and D received normal feed.

Samples of faeces were taken weekly using a sterile swab (Handi-Swab, Fisher) from the cloaca and cultured on MacConkey agar plates at 30 °C. These master plates were then replica plated on to MacConkey agar containing chloramphenicol and incubated at 30 and 42 °C. Table 1 illustrates the spread of the mutant plasmid from the initial two chickens to the rest of the animals in these cages. After 2 months, *E. coli* with temperature-sensitive chloramphenicol resistance were detected in 14% of chickens in cage A. Of particular note was the finding of *E. coli* with this particular *R* plasmid in faeces of 24% of chickens in a distant cage (B). None of the bacterial samples from chickens in cages not placed on tet-feed (C and D) demonstrated the mutant *R* plasmid.

Since only the plasmid was marked in this first experiment, a second study was carried out to determine whether the plasmid was being spread by way of the host bacterium. Plasmid *pSL222–6* was introduced into a mutant strain of chicken *E. coli* resistant to nalidixic acid (Nal^R). (Nal resistance is not normally found among *E. coli* in chicken gut flora.) The Nal^R *E. coli*-bearing *pSL222–6* were introduced by cloacal inoculation into four chickens previously fed tet-feed. These chickens were placed in a cage of 18 chickens also eating tet-feed and excreting organisms

Table 2 Spread of newly introduced R^+ *E. coli* among chickens

	Week 0	Week 1	Week 3	Week 4	Week 5
Number of new chickens excreting Nal^R *E. coli* (*pSL222–6*)	4	7	3	2	2
Accumulated number of chickens excreting Nal^R *E. coli* (*pSL222–6*)	4	11	14	16	18

Four chickens excreting Nal^R *E. coli* bearing temperature-sensitive chloramphenicol-resistant *R* plasmid *pSL222–6* were introduced into a cage of 18 chickens previously fed tetracycline and excreting tetracycline-resistant *E. coli*. Spread of Nal^R *E. coli* was followed by replica plating initial faecal samples, from MacConkey agar plates, on to (1) MacConkey agar + chloramphenicol at 30 and 42 °C; (2) MacConkey agar + nalidixic acid (30 μg ml^{-1}) at 37 °C. All Nal^R colonies were temperature sensitive for chloramphenicol and vice versa.

resistant to tetracycline, and the presence of the doubly marked *E. coli* followed (Table 2). After 1 week, 7 of the 18 chickens were excreting *Nal*^{R} *E. coli*, all of which showed temperature-sensitive chloramphenicol resistance. By 5 weeks these *E. coli* were detected in all the chickens in the cage. Spread was more rapid than in the previously described experiment. About 20–30% of *E. coli* in the flora of these animals was *Nal*^{R} (*pSL222–6*).

Over a two-month period faeces from eleven family members living on the farm and three laboratory workers responsible for the sampling of the chickens were tested for the presence of *pSL222–6*. On two occasions the plasmid was detected in human faeces. The first occurred in the faecal sample from the 12-yr-old son of the farm owner; 2 d after he had cleaned the cage in which chickens harbouring *E. coli* with this plasmid were housed, 78% of the coliforms in his faecal flora were resistant to chloramphenicol and this resistance was temperature sensitive. The *E. coli* also showed resistance to streptomycin and sulphonamides, but not to tetracycline. These resistances were not transferable. A similar non-transferable tetracycline-sensitive segregant of *pSL222–6* was found in *E. coli* from chickens in the cleaned cage. The presence of a plasmid in this *E. coli* was verified by the identification of a fast-moving peak of labelled DNA in an alkaline sucrose gradient (data not shown). Furthermore, other plasmids of the same incompatibility group (FII) were unstable when conjugated into this *E. coli*. This finding indicated the presence of a plasmid of the same incompatibility type as *pSL222–6*. Since typing of *E. coli* was not possible and the *E. coli* were not marked we could not determine whether the organisms were of human or chicken origin.

The second human host observed excreting *E. coli* with *pSL222–6* was an animal handler. One week after she had sampled chickens inoculated with the *Nal*^{R} *E. coli*-bearing *pSL222–6*, her faecal flora showed the presence of temperature-sensitive chloramphenicol-resistant *E. coli*. These *E. coli* were also resistant to nalidixic acid. All three other resistances on *pSL222–6* were also present. In conjugation the resistances in this *E. coli* were transferred together.

Subsequent faecal specimens from these two individuals 3 and 5 d after the initial sample did not reveal the presence of these particular organisms. Neither individual was taking antibiotics. Since only faecal swabs were examined, further studies would be necessary to determine whether these organisms were present to small extents in their intestinal tracts.

Our results demonstrate the spread of resistant organisms from chicken to chicken and from chicken to man. In studies of 1-d-old chicks, Smith[8] found *E. coli* from one group of chickens in faecal samples from a second group of chickens within 2 d of their being mixed in a cage. In the present study spread of the mutant *R* plasmid and *Nal*^{R} *E. coli* was detected in adult chickens in the same and distant cages. The mechanism of spread, whether by air or on the clothes of the feed handler, is not known. Cage-to-cage spread of bacteria is probably a common occurrence in a farm environment, followed by subsequent spread of plasmids and bacteria among the chickens in the cage.

In the light of our findings, transfer may also occur among other animals and between other animals and man. In the absence of direct contact and of selective pressure, such as that exerted by antibiotics, the frequency of spread is probably small. The subsequent transfer of animal *R* plasmids to human *E. coli* in the intestine, however, could occur[9] especially if the recipients were taking an antibiotic related to resistance determined by an *R* plasmid[10]. Although as few as 10^5 organisms can produce colonisation of the human intestinal tract[11] most studies *in vivo* have indicated that more than 10^9 bacteria need to be ingested[12,13]. This seems too many to have been ingested without their knowledge by the two individuals in this study. The results suggest a different route of entry or a different culture medium for the ingested bacteria, for example, by way of the nasal passages to sputum to the gastrointestinal tract.

These data bear on the widespread use of antibiotics in veterinary and medical practice and on the proposed use of *E. coli* as a vehicle in genetic engineering experiments. Further studies on the conditions affecting transfer and mixing between animal and human bacteria will be important in evaluating the consequence of antibiotic-resistant bacteria in animals in contact with man.

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The Molecular Relatedness of R Factors in Enterobacteria of Human and Animal Origin

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SUMMARY

The molecular length and DNA homology of R factors isolated from enterobacteria of human and animal origin have been examined. DNA from plasmids of the same compatibility group, whether of human or animal origin, is indistinguishable, after allowance has been made for the regions coding for different antibiotic resistances. These results indicate that there is a common pool of R factors in man and animals.

INTRODUCTION

Although it has long been postulated that R factors in man could be of animal origin (Anderson & Lewis, 1965*a*,*b*; Anderson, 1968*a*,*b*), this has been disputed (see, for example, Walton, 1966, 1970, 1975; Smith, 1969). Despite the similarity of many R factors identified in enterobacteria isolated from man and animals, no systematic scrutiny of such R factor has been carried out with the object of establishing the precise degrees of their genetic and molecular relatedness. The identification of several compatibility groups of R factors (Datta & Hedges, 1971; Hedges & Datta, 1971; Grindley, Grindley & Anderson, 1972; Smith, Humphreys & Anderson, 1974) and the establishment of the general rule that plasmids belonging to the same compatibility group have close molecular similarity (Guerry & Falkow, 1971; Grindley, Humphreys & Anderson, 1973) provided methods for determining the precise degree to which R factors (and other bacterial plasmids) of human origin are related to those found in animals. If the groups identified were the same in all species, they had a common origin; if they were dissimilar, they could have arisen independently in man on the one hand and in animals on the other.

METHODS

The plasmids investigated, and their sources, are shown in Table 1.

All the plasmids examined, code for drug resistance, with the exception of the Δ transfer factor of which the identified markers are its own transferability, the mobilization of resistance determinants, its fi⁻ and I-like nature, and the property of phage restriction in salmonellae and *Escherichia coli* K12 (Anderson & Lewis, 1965*b*; Anderson, 1966, 1968*b*). They belong to compatibility groups already studied genetically by Grindley *et al.* (1972), and in terms of DNA molecular homology by Grindley *et al.* (1973). Each group contained at least one factor of human and one of animal origin.

Seven of the 14 factors were apparently acquired by their carrier strains in England. The remaining seven were from widely separated geographical regions, although three of the

Table 1. *The plasmids studied and their origin*

Plasmid no.	Compatibility group	Resistances* and other markers	Origin: Organism	Origin: Place and date	Phage type	Organism of human or animal origin	Isolated from strain no.
240	FII	T, fi^+	*S. typhimurium*	England, 1963	29	Human	3M4466
R1-19K⁻		ACSSu, fi^-	*S. paratyphi B*	England, 1964	3a var 4	Human	8B7268
TP166		ACSSu, fi^+	*E. coli*	England, 1971	–	Bovine	EC11321
TP102	I_1	K, fi^+	*S. typhimurium*	England, 1968	Untypable	Human	8M5645
Δ		–, fi^-	*S. typhimurium*	England, 1964	29	Bovine	RT1
TP120	N	ASSuT	*S. typhimurium*	England, 1962	1a var. 2	Human	2M1818
TP158		ASSuT	*S. typhimurium*	Belgium, 1972	Untypable	Bovine	13M275
TP123	H_1	CSSuT	*S. typhi*	Mexico, 1972	Degraded Vi	Human	1T4739
TP153		CSSuT	*S. typhi*	Vietnam, 1974	E7	Human	1T5479
TP163		CSSuT	*S. typhi*	Thailand, 1974	53	Human	1T5688
TP171		CSSuT	*S. typhimurium*	England, 1972	Untypable	Bovine	12M974
TP154		AKT	*S. typhimurium*	Singapore, 1973	193	Avian	13M1653
TP116	H_2	CSSu	*S. typhi*	Spain, 1969	C1	Human	1T3616
TP167		CKST	*S. typhimurium*	Canada, 1974	186	Bovine	14M10

* Symbols for resistances: A, ampicillin; C, chloramphenicol; K, kanamycin; S, streptomycin; Su, sulphonamides; T, tetracyclines. All factors resistant to streptomycin were also resistant to spectinomycin, except TP167.

Table 2. *Contour lengths and molecular weights of the plasmids*

Plasmid		Isolated from strain of human (H) or animal (A) origin	No. of molecules measured	Mean contour length ± S.D. (μm)	10^{-6} × Molecular weight* (daltons)
Compatibility group	No.				
FII	240	H	13	19·8 ± 0·3	41·0
	R1-19K⁻	H	15	26·2 ± 0·5	54·2
	TP166	A	10	26·7 ± 0·6	55·3
I_1	TP102	H	15	28·5 ± 0·6	59·0
	Δ	A	30	28·7 ± 0·5	59·4
N	TP120	H	11	15·3 ± 0·2	31·7
	TP158	A	12	17·4 ± 0·2	36·1
H_1	TP123	H	12	59·5 ± 0·8	123·2
	TP153	H	10	55·2 ± 1·6	114·3
	TP163	H	10	55·5 ± 2·3	114·9
	TP171	A	12	58·5 ± 0·7	121·1
	TP154	A	10	61·3 ± 3·3	126·9
H_2	TP116	H	19	69·4 ± 1·5	143·7
	TP167	A	10	82·2 ± 3·7	170·2

* Calculated on the assumption that 1 μm of DNA = $2·07 \times 10^6$ daltons (Lang, 1970).

five H_1 factors came from salmonellae isolated in South East Asia (Anderson, 1975). The carrier strains were identified between 1962 and 1974.

The mutual incompatibility of plasmids within each group, and their compatibility with those of other groups, were established by the techniques of Grindley *et al.* (1972). The molecular properties and relationships were determined by the methods of Grindley *et al.* (1973). The standard carrier strain was K12F⁻ strain 703, or its nalidixic acid-resistant mutant 14R525.

RESULTS

Molecular size of the plasmids

Table 2 presents the contour lengths of the plasmids as determined by electron microscopy, and the calculated molecular weights. The molecular sizes of members of each group are of the same order, and the factors of human and animal origin in each group conform generally to the characteristic group size. The only possible exception to this was TP167, an H_2 factor from a strain of bovine *S. typhimurium* isolated in Canada. This factor was considerably larger than TP116, the only other H_2 representative studied, but its order of magnitude was closer to TP116 than to any of the factors of other groups. The H_2 plasmids are among the largest so far described.

The difference between the contour length of plasmid 240 (T resistance) and those of R1-19K⁻ and TP166 (ACSSu resistance) is probably caused by the presence of the ACSSu linkage group in the latter two plasmids. Dissociation of the ACSSu region from the complete R1-19K⁻ plasmid in *S. typhimurium* and *E. coli* reduces the length of the plasmid by 7 μm to about 19 μm (Cohen & Miller 1969; Humphreys, Willshaw and Anderson, unpublished).

DNA reassociation studies

The results shown in Table 3 and Fig. 1 establish clearly the close relationship between the DNA of plasmids of each compatibility group: the homology was always more than 50 %, and usually much higher. In contrast, little homology was evident with plasmids of

Table 3. *Homology between plasmids of animal and human origin*

The values indicate the degree of reassociation at 75 °C of ^{3}H-labelled plasmid DNA with unlabelled plasmid DNA relative to the reassociation both with DNA of the same plasmid (= 100) and with *E. coli* K12 chromosomal DNA (= 0).

Unlabelled DNA from strains bearing plasmids			Labelled plasmid DNA											
			FII			I_1		N		H_1			H_2	
Group	Human (H) or animal (A) origin	Plasmid no.	240	R1-19K⁻	TP166	TP102	Δ	TP120	TP158	TP123	TP153	TP154	TP116	TP167
FII	H	240	100	57	54	14	13	0	0	3	—	4	0	3
	H	R1-19K⁻	—	100	93	—	—	—	—	17	—	—	—	—
	A	TP166	64	85	100	9	10	10	—	17	6	5	9	4
I_1	H	TP102	13	—	11	100	75	7	4	2	—	3	—	—
	A	Δ	15	—	11	65	100	1	0	—	—	4	0	0
N	H	TP120	1	—	4	0	1	100	94	5	—	0	0	2
	A	TP158	1	—	3	1	0	101	100	10	—	—	—	—
H_1	H	TP123	10	17	24	0	0	9	6	100	91	91	8	0
	H	TP153	—	6	12	—	—	—	3	94	100	95	5	0
	H	TP163	10	6	9	1	0	8	4	88	96	82	7	5
	A	TP171	—	—	—	—	—	—	—	—	100	—	—	—
	A	TP154	6	0	8	0	0	7	12	87	92	100	0	0
H_2	H	TP116	2	—	—	—	0	8	—	4	0	—	100	65
	A	TP167	—	—	—	—	—	—	—	—	0	—	81	100

The broken line encloses reactions of labelled plasmid DNA with unlabelled plasmids from the same compatibility group.
—, Not done.

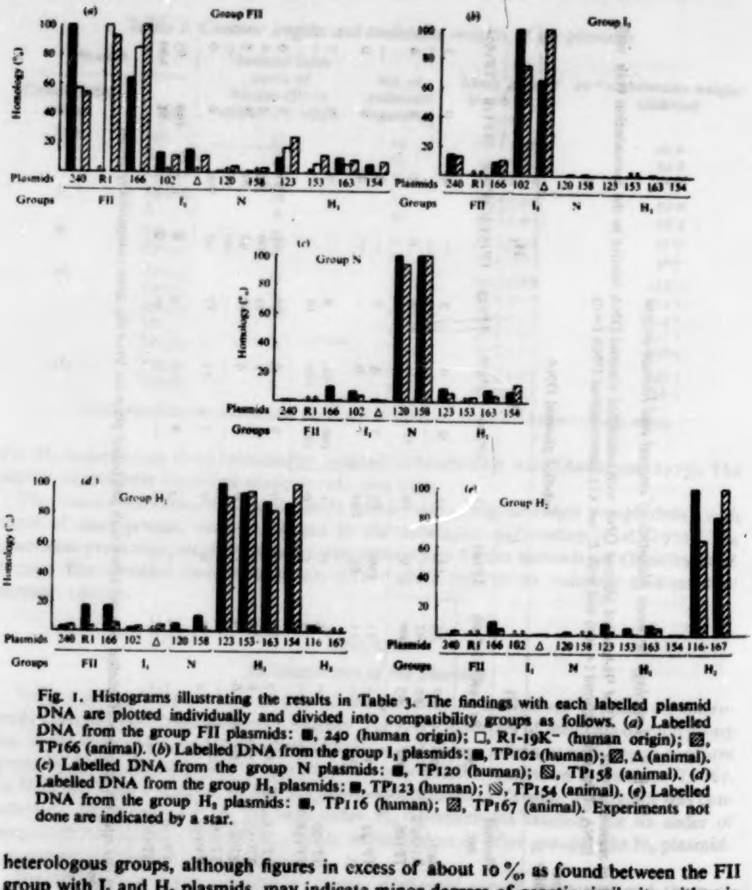

Fig. 1. Histograms illustrating the results in Table 3. The findings with each labelled plasmid DNA are plotted individually and divided into compatibility groups as follows. (*a*) Labelled DNA from the group FII plasmids: ■, 240 (human origin); □, $R1\text{-}19K^-$ (human origin); ▨, TP166 (animal). (*b*) Labelled DNA from the group I_1 plasmids: ■, TP102 (human); ▨, Δ (animal). (*c*) Labelled DNA from the group N plasmids: ■, TP120 (human); ▧, TP158 (animal). (*d*) Labelled DNA from the group H_1 plasmids: ■, TP123 (human); ▧, TP154 (animal). (*e*) Labelled DNA from the group H_2 plasmids: ■, TP116 (human); ▨, TP167 (animal). Experiments not done are indicated by a star.

heterologous groups, although figures in excess of about 10 %, as found between the FII group with I_1 and H_1 plasmids, may indicate minor degrees of genetic similarity, either in regions determining antibiotic resistance or in other, unidentified, regions. The outstanding feature of these studies, however, was the close correspondence between the nucleotide sequences of the plasmids of human and of animal origin in each compatibility group.

DISCUSSION

The high degree of DNA homology between the auto-transferable plasmids isolated from the enterobacteria of man and of animals establishes unequivocally that in all important respects these plasmids are identical. It can therefore be concluded that they are drawn from a common pool. Differences in genetic markers, such as those for drug resistance, between members of the same group do not affect this argument, because the resistance determinants emerge in response to pressure by a range of antibiotics. Although they recombine with the respective transfer factors to form R factors, they are of independent origin and may indeed represent the only disparity between the DNA of members of a given compatibility group. Moreover, the same resistances are found in man as in animals, in members of each plasmid compatibility group.

The question that naturally arises is: which is the direction of flow of R factors and other plasmids – from animals to man or vice versa? Man must contribute to the plasmids of animals, but the opportunity for flow in the opposite direction is probably much greater, bearing in mind the environmental contamination with animal enterobacteria which results from poor food hygiene, the handling of uncooked meat, and the consumption of inadequately cooked meat products. The continuous occurrence of outbreaks of salmonella food poisoning, in which the salmonellae concerned frequently carry R factors they are known to have acquired in animals, suggests that the animal contribution may be substantial (Anderson & Lewis, 1965*a*,*b*; Anderson, 1968*a*,*b*). However, these are special cases, and the extent to which animals are a source of R factors in man cannot easily be determined. Unless plasmid-bearing non-pathogenic enterobacteria such as *E. coli*, of animal origin, can be identified with certainty in man, this problem may remain largely unsolved, since enterobacteria of animal origin, which do not establish themselves in the human intestine, may nevertheless transfer their plasmids to the resident human enterobacteria before disappearing (Anderson, 1968*c*).

A drastic cutback in the use of antibacterial drugs would probably result in a reduction in the size of the reservoir of resistance plasmids. But *E. coli* carrying R factors are present and apparently stable in many persons who have never been treated with antibiotics (Anderson, Gillespie & Richmond, 1973; E S. Anderson, unpublished). This indicates that once some R factors, from either animal or human sources have gained entry to the enterobacterial population, maintenance of antibiotic pressure is unnecessary for their persistence. Whether total cessation of the use of antibacterial drugs would ultimately result in a massive reduction in the distribution of these plasmids is an unanswerable question, because such cessation cannot be achieved. Indeed, even partial withdrawal is unlikely, though a temporary local withdrawal of the type described by Price & Sleigh (1970) and Lowbury, Babb & Roe (1972) can be an effective solution to problems of hospital infection with drug-resistant opportunist pathogens in individual units or areas. Continuous international monitoring of the distribution of R factors and other plasmids in man and animals is necessary, so that information on this vitally important aspect of human and animal ecology is constantly available.

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Emergence of Antibiotic-Resistant Bacteria in the Intestinal Flora of Farm Inhabitants

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The frequency with which antibiotic-resistant bacteria are encountered in our environment continues to be a cause of much concern. Although most of these resistant bacteria are themselves nonpathogenic, they pose the threat of potential transfer of their resistance factors to pathogenic species. Furthermore, since antimicrobial drugs are used in animal and plant medicine, the spread of selected resistant organisms from one host to another may be important. The genetic information for antibiotic resistance is carried on R plasmids (R factors), which are pieces of extrachromosomal DNA. Many of these plasmids can be transferred between different species of bacteria [1]. Bacteria of all species may contain plasmids, and many different properties are encoded by plasmid DNA [2].

Antibiotics select resistant bacteria in animals, plants, and humans to whom the drug has been administered. Evidence has suggested animal-to-human spread of resistant bacterial strains and/or antibiotic resistance, but no clear cause-and-effect relationship between drug-supplemented animal feed and the presence of resistant bacteria in humans has been shown. We therefore decided to examine the effect of oxytetracycline-supplemented feed on the fecal flora of a farm family in contact with both chickens given oxytetracycline-supplemented feed and the feed itself [3].

Experimental Information

Three hundred twenty-five Leghorn one-day-old chickens were received on a private farm and raised together for two months. They were then tagged, and approximately 50 chickens were placed into each of six cages. The resident farm family consisted of two parents and nine children (four to 20 years old). Five families, 24 individuals in all, living within an 8-km radius of the farm acted as the local control group. Ten medical students of Tufts University Medical School (Boston, Mass.) were the urban control group.

Fecal specimens were taken weekly by swabbing of the cloaca of the chicken. Each chicken was sampled approximately once every other week. Human fecal specimens were also obtained weekly with sterile swabs. The organisms were identified and classified by use of selective plates and routine biochemical methods [3]. Antibiotic disks were used to test for antibiotic sensitivity. The coliform bacteria were examined for pattern and type of resistance.

Upon reaching three months of age, chickens in the test group were given oxytetracycline-supplemented feed; a control group received normal feed. The amount of tetracycline in the feed was at levels used for therapy and prophylaxis.

Results

Escherichia coli, *Proteus mirabilis*, and enterococci were the main organisms obtained from aerobic cultures of chicken and human feces before the experiment began. Among the Enterobacteriaceae, *E. coli* was by far the predominant species. The fecal flora of individual chickens contained 0.1%–10% tetracycline-resistant organisms.

Within 36 hr of initiation of drug-supplemented feeding, essentially all of the *E. coli* and *P. mirabilis* from the intestinal tract of the chickens given oxytetracycline-supplemented feed were tetracycline-resistant. No change in the frequency of organisms was observed. Chickens in the control group maintained a low percentage of antibiotic-

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Table 1. Prevalence of tetracycline resistance among organisms isolated from fecal swab samples.

Group	No. of subjects	No. of samples	Percentage of samples with indicated frequency of tetracycline-resistant bacteria		
			<20%	21%–80%	81%–100%
Farm family	11	83	51.8	16.8	31.3
Neighbors (local control)	24	189	82.0	11.0	6.8
Boston students (urban control)	10	65	93.9	3.0	3.1

resistant intestinal bacteria until the fourth month following the introduction of the supplemented feed, at which time > 30% of the chickens had > 50% resistant bacteria.

During the initial 12-week period, there was little change in the tetracycline resistance of the fecal flora of the family members or of their neighbors. After this period, however, the number of tetracycline-resistant bacteria began to increase in the farm group. Between four and six months after the drug-supplemented feeding was begun on the farm, a dramatic increase was noted in the tetracycline resistance of the intestinal bacteria obtained from the fecal material of farm personnel (table 1). While neighbors and urban control groups showed consistently low levels of resistant *E. coli*, the level of resistant bacteria greatly increased among farm members. Thirty-one percent of weekly samples from farm members were almost completely resistant to tetracycline. Resistance to six other antibiotics unrelated to tetracycline also increased. No similar increase in resistance to other antibiotics was found in the fecal flora of their neighbors.

After prolonged use of the oxytetracycline-supplemented feed, both the chickens and the farm family showed increased numbers of *E. coli* carrying multiple resistances. After two months, > 20% of the *E. coli* from chickens fed the supplemented feed demonstrated resistance to antibiotics other than tetracycline, including streptomycin, ampicillin, carbenicillin, and sulfonamides. Four months after the feeding was begun, 36% of the bacterial samples from the farm family demonstrated resistance to three or more antibiotics. Similar evidence of multiple resistance was found in only 6% of the samples taken from their neighbors.

Bacterial matings were peformed to determine whether the genes mediating antibiotic resistance were transferable to other *E. coli*. In human and chicken *E. coli*, the transfer of tetracycline resistance alone was only rarely achievable. When this resistance gene became associated with other resistances, its transfer was more frequent (table 2). In general, more than one of the resistances harbored by the animal or human bacteria were simultaneously transferable; only some were transferred independently [4].

In another study, a plasmid bearing a temperature-sensitive chloramphenicol resistance marker was introduced into *E. coli* isolated from the chickens. These *E. coli* were fed to chickens which were placed into cages with control chickens. In the presence of oxytetracycline-supplemented feed, these strains spread from the test chickens to other chickens in the same cage and also to chickens in a cage at a distance from them [5]. No such spread was found in chickens not given the supplemented feed. Thus oxytetracycline-supplemented feed not only selected for resistant bac-

Table 2. Transfer of resistance to tetracycline when associated with resistance to other antibiotics in the same host *Escherichia coli*.

Resistance in host *E. coli*	Strains isolated from	
	Humans	Chickens
Tc	0/7	4/41
TcSu	0/3	. . .
TcSm	3/3	10/14
TcSmNeo	0/4	. . .
TcCmNeo	2/2	. . .
TcSmSu	5/10	3/10
TcAmpCarbSu	3/3	. . .
TcCmSmSu	4/7	. . .
TcAmpCarbSmSu	5/6	15/15*
TcAmpCarbSmSuNeo	9/9	. . .

NOTE. Data are number of strains transferring tetracycline resistance/number of strains tested. Tc = tetracycline, Su = sulfonamides, Sm = streptomycin, Neo = neomycin, Cm = chloramphenicol, Amp = ampicillin, and Carb = carbenicillin.

*Did not contain sulfonamide resistance.

teria but also promoted the spread of resistant organisms among chickens in the same, as well as in different, cages. More important, these marked chicken bacteria were found in the feces of two persons in contact with the chickens [5]. These findings clearly indicated a chicken-to-human transmission of resistant bacteria.

Tetracycline resistance in the fecal flora of the chickens given oxytetracycline-supplemented feed persisted for at least two months after the feeding was discontinued and the cages were cleaned. Only when the antibiotic-fed chickens were put in contact with chickens harboring sensitive *E. coli* did the levels of resistant *E. coli* diminish in the antibiotic-fed birds [4]. Stools from the human farm dwellers were tested six months after the removal of all tetracycline-supplemented feed from the farm, and in most cases no detectable tetracycline-resistant organisms were found.

Conclusions

An increase in antibiotic-resistant intestinal bacteria was found in a farm family in contact with both tetracycline-fed chickens and the oxytetracycline-supplemented feed. Within three to five months following the introduction of the feed, a similar change was noted in the chickens of the control group and in the farm personnel as well. We propose two possible explanations for these findings: human contact with tetracycline in the feed and environment, and transfer of resistant organisms between chickens and humans, aided by the selective influence of tetracycline in the environment. This apparent selection for resistant organisms was reversible after nine months of usage of the supplemented feed, since resistant organisms were not found six months after discontinuation of the supplemented feed at the farm.

While no sickness associated with resistant bacteria occurred during the time of this study, it has been clearly demonstrated that use of the supplemented feed increased the pool of transferable resistance genes. Furthermore, the use of only one antibiotic (tetracycline) led to the selection of bacteria resistant to many different antibiotics, this resistance being carried by transferable plasmids. The transfer of these plasmids from nonpathogenic to pathogenic bacterial strains, and from animals to humans, is a potential consequence of the widespread use of antibiotics in the farm environment, as well as in other settings. Critical evaluation of these sequelae of antibiotic usage is necessary. The data from this and other studies [6, 7] argue strongly against the present-day practice of unqualified and unlimited use of antibiotic-supplemented feeds in animal husbandry.

We have observed a high frequency of antibiotic-resistant bacteria in our environment. Although the use of a vector for recombinant DNA studies with an antibiotic resistance marker would seem to add little to the pool of resistance genes already present in nature, we must, on the other hand, bear in mind that antibiotic usage is widespread and that the drugs themselves are major selective forces for resistant organisms. Thus, if a recombinant vector with a resistance marker were to escape into the environment, it would then have a better chance for survival, an undesirable feature. Therefore, antibiotic markers of commonly prescribed drugs should not be used on vectors for recombinant DNA research.

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CHANGES IN INTESTINAL FLORA OF FARM PERSONNEL AFTER INTRODUCTION OF A TETRACYCLINE-SUPPLEMENTED FEED ON A FARM

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Abstract A prospective study was undertaken to determine whether feeding farm animals antibiotics in feed caused changes in the intestinal bacterial flora of farm dwellers and their neighbors. Chickens were fed tetracycline-supplemented feed (tet-feed), and, as expected, within one week their intestinal flora contained almost entirely tetracycline-resistant organisms. Increased numbers of resistant intestinal bacteria also appeared, but more slowly, in farm members, but not their neighbors. Within five and six months, 31.3 per cent of weekly fecal samples from farm dwellers contained >80 per cent tetracycline-resistant bacteria as compared to 6.8 per cent of the samples from the neighbors (P<0.001). Seven of the 11 farm members, but only three of the 24 neighbors, had two or more fecal samples containing >80 per cent tetracycline-resistant coliforms (P<0.01). These resistant bacteria contained transferable plasmids conferring multiple antibiotic resistances. Selective pressure by tet-feed for antibiotic-resistant bacteria in chickens extends to human beings in contact with chickens and the feed. (N Engl J Med 295:583-588, 1976)

THE prevalence of antibiotic-resistant bacteria in the environment has caused widespread concern.[1,2] Besides the difficult problem of treating clinical infection caused by antibiotic-resistant organisms, there is the threat posed by the potential transfer of resistances from nonpathogenic to pathogenic bacteria. The genetic information for antibiotic resistance resides primarily on extrachromosomal DNA elements, called R plasmids (R factors), many of which can be transferred from bacterium to bacterium even between different bacterial species.[3] Numerous reports in the literature have demonstrated the worldwide prevalence of resistance plasmids in bacteria in hospitalized and ambulatory persons,[1,4-6] in domestic and farm animals[1,7,8] and in food products.[9-12]

Antibiotics select for resistant bacteria in the animals and human beings taking the drug.[1,13,14] Many of these resistances are present on transferable plasmids. It has been suggested that one factor contributing to increased resistant bacteria in human beings is the selective pressure of antibiotics in animal feeds.[1,2,7,15,16] Anderson and Lewis linked an antibiotic-resistant *Salmonella typhimurium* to infection in cattle and human beings.[17] Evidence has suggested animal-to-human spread of resistant bacteria,[1,2,7,15] and this possibility has recently been documented with use of a biochemically marked plasmid and host bacterium.[18] However, a cause-and-effect relation between animal drug feeds and antibiotic-resistant strains in human beings is unclear, since antibiotics in different forms are used so frequently in animal and human groups.

To examine in a controlled manner what effect an antibiotic-supplemented feed given to animals had on the farm inhabitants, we designed the present study and recorded the changes in bacterial intestinal flora of chickens, farm dwellers and their neighbors before and after the introduction of a tetracyciane-supplemented feed to the farm.

MATERIALS AND METHODS

Animals

Three hundred and twenty-five one-day-old Leghorn chickens purchased from SPAFAS (Connecticut) were received on a private farmstead in Sherborn, Massachusetts, on July 1, 1974. No antibiotic-containing feed products had been used in the area during at least the previous seven-year period. The chickens were raised to one month in a small brooder (1.4 m²) heated with accessory lamps. They were maintained in the absence of antibiotics. Over 90 per cent of the chickens lived and were vaccinated twice against respiratory virus during this time. The vaccine was prepared without the antibiotics (penicillin and streptomycin) that are routinely added to commercial vaccines. Animals were fed commercial starter mash (Farm Bureau brand) for the first month. This feed contained the coccidiostat amprolium (0.005 per cent) and bacitracin. After the first month, the chickens were given a pullet developer (Purina) that contained no drugs. Each new lot of feed was tested for the absence of antibiotic activity by extraction of 1 g of feed with 5 ml of water and study of this extract for inhibition of growth of sensitive *Escherichia coli* on nutrient agar plates. From the age of three months, chicken feed with and without tetracycline (oxytetracycline) (100 g per 909 kg) (Pfizer) was given. Only extracts of the tet-feed showed antibacterial activity.

Human Subjects

The resident farm family consisted of two parents and nine children (4 to 20 years old). Five families (24 members, including 10 adults and 14 children) living within an 8-km radius of the farm, without direct contact with the chickens or with any antibiotic-supplemented feed, acted as a control group. Two people in the laboratory, and 10 volunteer Tufts University Medical School students also participated in the study; none of them were taking antibiotics.

Distribution of Chickens on the Farm

At two months of age the chickens were placed into six newly-constructed cages (9.4 m², approximately 50 chickens per cage). Four groups were raised inside a barn of 900 m², and two groups were housed outside. At each end of the 60-meter-long barn two cages were constructed approximately 15 meters apart. Males and females were evenly distributed. Each chicken was identifiable by a number tagged to its foot. Chickens housed in two cages at one end of the barn and in one cage outside the barn were placed on tet-feed during the course of the study.

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Stool Sampling and Plating

We obtained samples of chicken feces by introducing and rotating a sterile moistened swab (Handi Swab, Fisher Scientific) 6 to 8 cm into the cloacus of the chicken. The swab was placed in holding medium (Stuart's medium) for delivery to the laboratory for plating. These specimens were streaked onto MacConkey, phenyl ethyl alcohol and Hektoen plates and incubated at 30 to 37°C for 18 to 24 hours. Approximately one quarter to one half of the chickens in a cage were sampled each week. In general each chicken was sampled every other week. Human fecal specimens were also obtained with use of the sterile swab. Chicken fecal samples were plated within two to six hours after being obtained; human specimens were plated within two to 12 hours. Prior studies in the laboratory indicated that samples plated during this period did not differ from those plated immediately. Since most of the stool samples were taken from the anal canal, not directly from a stool sample, this method of sampling was compared with direct sampling of feces. No difference in numbers or kinds of bacteria was observed between two fecal samples taken from the same chicken and held in holding medium: one taken immediately after excretion and the other obtained by cloacal swab. Likewise, no difference was observed in the bacterial flora or the antibiotic-resistance pattern when three fecal specimens from the same human subject were compared: one plated immediately after excretion; one stored in holding medium for one hour at 25°C, and one taken from the rectum before the stool was passed and also stored in holding medium for one hour at 25°C. Within the limits of individual stool specimens, then, the method of obtaining the specimen appeared valid for that time and day.

To test the possibility that R plasmid-containing bacteria were unable to convert from anaerobic in vivo conditions to aerobic culture conditions for testing, animal fecal specimens were incubated in duplicate under aerobic or anaerobic conditions. The same numbers of colonies and the same resistance patterns were found aerobically and anaerobically on MacConkey agar plates. Aerobic and anaerobic analysis of fecal samples containing large numbers of R plasmid-containing *Esch. coli* showed no differences. R plasmids did not influence the ability of *Esch. coli* to convert to aerobic conditions.

Bacteriology

Routine bacteriologic analyses to identify organisms were performed on all fecal specimens from the chickens and human beings living on the farm.[18] In the initial bacterial studies two to four morphologically different colonies representing the predominant organisms were isolated from each of the three selective plates. These organisms were identified and classified by means of biochemical methods and were subsequently characterized for antibiotic sensitivity with use of antibiotic disks (Pfizer Diagnostics) on Mueller–Hinton plates.[20] Antibiotic sensitivity was tested to ampicillin (10 μg), carbenicillin (50 μg), chloramphenicol (5 μg and 30 μg), cephalothin (30 μg), streptomycin (10 μg), tetracycline (5 μg and 30 μg), sulfonamides (300 μg), trimethoprim-sulfamethoxazole (25 μg), gentamicin (10 μg) and neomycin (5 μg). When tet-feed was introduced on the farm, bacterial samples were replica-plated[19] onto MacConkey agar supplemented with tetracycline (25 μg per milliliter). By two-dimensional dilutional spreading of the initial stool specimen on the MacConkey plate, several hundred colonies could be observed and replica-plated, and the percentage of tetracycline-resistant organisms could be determined.

Characterization of Antibiotic Resistance

The patterns and types of antibiotic resistance were checked in coliforms. The transferability of drug resistances in *Esch. coli* was determined by overnight bacterial mating. The recipient was DO-11, a nalidixic acid-resistant derivative of *Esch. coli* CSH-2. Donor (final concentration 1.5×10^7 per milliliter) and recipient (final concentration 1.5×10^8 per milliliter) were incubated together overnight at 37°C in 10 ml of nutrient broth. The mixture was subsequently plated onto different selective plates to examine transfer of individual resistances. Recombinants were checked for coincident transfer of other resistance markers.

RESULTS

Changes in Intestinal Flora after Introduction of Tet-Feed

Before tet-feed was given, *Esch. coli*, *Proteus mirabilis* and enterococci were the predominant organisms obtained from aerobic cultures of chicken and human feces. The relative quantities of each varied, but in both chicken and human specimens, *Esch. coli* was predominant (80 to 90 per cent) among the enterobacteria. Other enterobacteria in the chicken cultures included *Klebsiella pneumoniae*, *Enterobacter agglomerans*, pseudomonas and acinetobacter. No salmonella was detected. Other organisms obtained from human beings were *K. pneumoniae*, *Citrobacter freudi*, *Enterobacter cloacae* and *hafniae*, *Proteus rettgeri* and acinetobacter.

The feces of chickens contained low numbers of organisms resistant either to tetracycline, streptomycin or sulfonamides. Of the *Esch. coli* generally less than 10 per cent were resistant to tetracycline, and many fecal samples contained less than 0.1 per cent tetracycline-resistant organisms. Among farm personnel and neighbors the numbers of tetracycline-resistant organisms were relatively low from the beginning of the study. Over 90 per cent of the fecal samples contained less than 10 per cent tetracycline-resistant *Esch. coli*, and most of them had levels less than 0.1 per cent. All proteus and enterococci were resistant to tetracycline.

The tet-feed was received on the farm in September, 1974, and was given to the chickens during the second week of October. The amount of tetracycline in the feed was at a level used for therapy or prophylaxis. The intestinal flora of chickens changed rapidly within 36 to 48 hours from low numbers of resistant organisms to high numbers (>60 per cent) with tetracycline resistance. Within two weeks 90 per cent of the chickens were excreting essentially all tetracycline-resistant organisms. No change in the frequency of organisms was observed: *Esch. coli* remained predominant. Chickens not fed tet-feed maintained low numbers of resistant intestinal bacteria until four months after tet-feed was introduced into the barn, when the intestinal flora of over 30 per cent of the chickens inside the barn contained >50 per cent resistant bacteria. Bacteria were observed that were resistant to antibiotics other than tetracycline, including ampicillin, carbenicillin, streptomycin and sulfonamides. All chickens in the same cage had *Esch. coli* with similar antibiotic-resistance patterns, but patterns and frequencies differed among the cages.

During the first three months after introduction of tet-feed, monthly samples from the family and neighbors showed little difference in the number of individual samples containing high numbers (>80 per cent) of tetracycline-resistant organisms. However, the average number of tetracycline-resistant bacteria was higher in the farm group. In January the fecal samples from three of eight family members contained >80 per cent tetracycline-resistant bacteria with an average number of resistant organisms in fecal samples from the family members of 36 per cent. In contrast, only one of 15 neighbors sampled was excreting high numbers of resistant bacteria, and the average number of resistant organisms in this group was <10 per cent.

To control for seasonal variation and to assess at a period more regular than once a month, weekly samples were taken from the farm family and neighbors during the fifth and sixth months (March and April) after introduction of tet-feed to the chickens. Each subject was sampled at least six times, and in most cases for nine weeks. Ten members of the first-year Tufts medical-school class and two members of the Tufts laboratory in Boston were similarly tested and served as controls outside the community. The results showed increased tetracycline resistance in the intestinal bacteria from farm personnel (Fig. 1). Of the 83 fecal samples received from the 11 members of the farm family, 31.3 per cent contained >80 per cent tetracycline-resistant organisms, primarily *Esch. coli*. In contrast, 0 to 12.1 per cent of the samples from any neighboring family showed high numbers (>80 per cent) of resistant organisms, and the average from all the neighboring families was 6.8 per cent. Furthermore, the overall number of tetracycline-resistant organisms in the samples from the neighbors was lower than that in those from the farm. Samples from the Boston group closely resembled those of the Sherborn neighbors in that only 3.8 per cent of the samples showed >80 per cent organisms resistant to tetracycline. Assuming that each sample is independent, the probability of getting a result this extreme is <0.001.

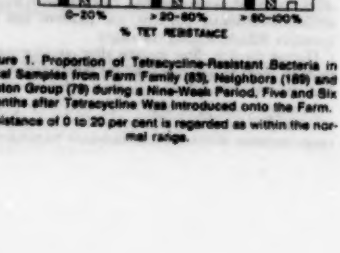

Figure 1. Proportion of Tetracycline-Resistant *Bacteria* in Fecal Samples from Farm Family (83), Neighbors (189) and Boston Group (79) during a Nine-Week Period, Five and Six Months after Tetracycline Was Introduced onto the Farm.

Resistance of 0 to 20 per cent is regarded as within the normal range.

Seven of the farm personnel and family members produced two or more fecal samples with >80 per cent tetracycline-resistant organisms as compared to only three of 24 neighbors (P<0.01). Moreover, four of the subjects on the farm, but only one of the neighbors, had consecutive weekly elevated numbers (>80 per cent) of tetracycline-resistant bacteria.

Emergence of Multiply Resistant Bacteria in Chickens and Human Beings after Exposure to Tet-Feed

With lengthened time of exposure of chickens to tet-feed, there was an increased frequency of *Esch. coli* carrying resistance to unselected antibiotics, including streptomycin, ampicillin, carbenicillin and sulfonamides (Fig. 2). Resistance to ampicillin and carbenicillin was not detected in chickens before their ingestion of tet-feed and was found only in chickens housed inside the barn. Multiple resistance was found in more than 50 per cent of the *Esch. coli* strains from chickens eating tet-feed for more than 10 weeks. After two months on tet-feed, over 20 per cent of the *Esch. coli* organisms from chickens inside the barn carried the pattern of resistance to tetracycline, ampicillin, carbenicillin and streptomycin. In the outside cage, over 25 per cent of bacteria cultured from tetracycline-fed chickens showed resistance to tetracycline in association with streptomycin and sulfonamides.

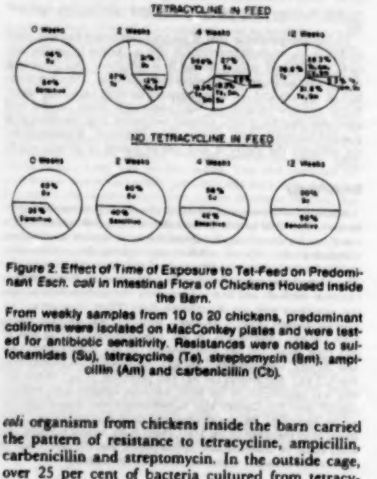

Figure 2. Effect of Time of Exposure to Tet-Feed on Predominant *Esch. coli* in Intestinal Flora of Chickens Housed inside the Barn.

From weekly samples from 10 to 20 chickens, predominant coliforms were isolated on MacConkey plates and were tested for antibiotic sensitivity. Resistances were noted to sulfonamides (Su), tetracycline (Te), streptomycin (Sm), ampicillin (Am) and carbenicillin (Cb).

Similarly, increased multiply resistant *Esch. coli* were noted in the farm dwellers, but not in neighbors, during the later months of tet-feed administration on the farm (Table 1). Over the period examined, 36 per cent of bacteria from the farm family showed resistance to three or more antibiotics, as compared to 6

Table 1. Antibiotic-Resistance Pattern of *Esch. coli* Strains Cultured from Feces.*

Mo	No. of People Sampled	Total Samples	Sensitive Strains	No. of Resistant Strains: Te	N	Sm	Te Sm	Te Su	Sm Su	Am Cb	Te Sm Su	Te Sm N	Sm Cm Su	Te Sm Su N	Te Am Cb Sm	Am Cb Sm Su	Te Am Cb Sm Su	Te Am Cb N Sm Su	Te Am Cb Sm SXT Su
Farm family:																			
Oct	6	6	2	2		1	1												
Nov	8	13	6	1	1	2										1	1	1	
Dec	9	17	5		1		2									3	2	2	2
Jan	10	20	9		2	1	1					1			1	2	3		
Feb	8	14	4	3		1							1			4	1		
Totals		70	26	6	4	5	4	0	0	0	0	1	1	0	1	10	7	3	2
Neighbors:																			
Oct	12	14	10				2		1					1					
Nov	3	4	2							2									
Dec	7	13	8					1		4									
Jan	15	26	22				1		1	1	1								
Feb	5	9	6							1	2								
Totals		66	48	0	0	0	3	1	2	8	3	0	0	1	0	0	0	0	0

*Te denotes tetracycline, N neomycin, Sm streptomycin, Su sulfonamides, Am ampicillin, Cb carbenicillin, Cm chloramphenicol, & SXT trimethoprim + sulfamethoxazole.

per cent from the neighbors. Resistance to more than four drugs was found only in farm dwellers. During October to February only 18 of 41 (44 per cent) of predominant *Esch. coli* strains isolated from the farm family were sensitive to antibiotics in contrast to 34 of 42 (81 per cent) from neighbors.

Transferability of Antibiotic Resistance in Chickens and Human Beings

Bacterial matings were performed to determine whether the genes mediating resistance were transferable to other *Esch. coli*. Tetracycline resistance when found alone in *Esch. coli* in chickens or human beings was rarely transferable. Only four of the 41 isolates from chickens tested showed transfer, and none of 17 isolates from human subjects. As this resistance gene became associated with other resistances, its transfer became more easily detected. When associated with streptomycin resistance in *Esch. coli* from chickens, tetracycline resistance transferred from about 70 per cent of the donors, approximately half the time with streptomycin resistance (Table 2). Transfer of the tetracycline resistance gene was not detected when in combination with sulfonamide resistance, but transfer was detected from about 30 per cent of the donor bacteria when in combination with resistance to streptomycin and sulfonamides. When associated with resistance to streptomycin, ampicillin and carbenicillin, tetracycline resistance was transferred from every donor tested. All resistant organisms were transferred from the donor en bloc, indicating their presence on a single R plasmid.

Table 2. Transfer of Antibiotic Resistance from *Esch. coli* Isolated from Chickens.*

Resistance Pattern	No. of Strains Tested	Resistance Transferred
Te	41	Te(4)† 9.7%
Sm	4	Sm(2) 50%
Te, Sm	14	Te(2) 14.3%; TeSm(8) 57%
Te, Su	12	(0) <8%
Te, Sm, Su	10	TeSm(3) 30%
Te, Sm, Am, Cb	15	TeSmAmCb(15) 100%

*Te denotes tetracycline, Sm streptomycin, Su sulfonamides, Am ampicillin, & Cb carbenicillin.

†Figures in parentheses represent no. of strains.

A more varied pattern of antibiotic resistance was seen in the human samples (Table 1); however, *Esch. coli* strains were found with resistance patterns similar to those observed in chickens. In general, one or more of the resistances were transferable; in many, resistances were transferred separately. Tetracycline and streptomycin resistances were transferred together, as was seen in the *Esch. coli* from chickens. Ampicillin resistance, found in combination with resistance to many other antibiotics, was transferred over 90 per cent of the time, always in association with carbenicillin resistance.

Effect of Eating Eggs from Tet-Fed Chickens on Consumers' Intestinal Flora

Over a two-month period beginning four months after introduction of the tet-feed, three neighbor families (18 family members) consumed eggs daily only from tet-fed chickens whereas two neighbor families (six members) received eggs from non-tet-fed chickens. Boston consumers ate commercial eggs. No effect on intestinal flora was noted from ingestion of eggs from tet-fed chickens: no change or difference in flora was found between the two groups. Eggs carefully washed before distribution were also tested for presence of resistant organisms on the shells; none were found.

Effect of Removal of Tet-Feed from the Farm on the Intestinal Flora of Farm Dwellers

To evaluate the reversibility of the increased number of tetracycline-resistant organisms found in farm dwellers, we recultured stools of 10 of the farm residents twice during the third week of January, 1976, six months after removal of all tet-feed from the farm. Duplicate samples were the same. No detectable tetracycline-resistant organisms (<1 per cent) were found in the intestinal flora of eight out of 10 subjects; one had 5 per cent resistant organisms, and 1 had >80 per cent. These frequencies were much lower than those found before removal of the tet-feed and lower than that found in January of the previous year. They resembled those found in the neighbor population.

DISCUSSION

An increase in resistant intestinal bacteria was found in farm dwellers in contact with tetracycline-fed chickens and the tet-feed. Although this change was seen in the chickens within a week of tetracycline ingestion, it was not obvious in the farm personnel until three to five months after tet-feed was introduced on the farm. Similarly, chickens maintained on tet-free feed inside the barn did not show a change in flora until four to five months after introduction of tet-feed on the farm. The gradual increase in resistance in this non-tet-fed group presumably indicated exposure with time to the antibiotic on the farm. Since the most notable change in human flora was an increase in the number of fecal samples containing almost entirely (>80 per cent) tetracycline-resistant organisms, and since the resistant organisms cultured from the human subjects did not all show the same resistance patterns as those from chickens, we assume that this conversion to resistance resulted from contact with tetracycline in the feed and environment. Transfer of resistant organisms between chickens and man, aided by the selective influence of tetracycline in the environment, could also have contributed.[18]

During the same test period, low numbers of resistant organisms were found in two control groups: neighbors living in the same area and attending the same schools, but with little contact with the animals or feed; and an urban (Boston) group not directly exposed to antibiotics. The fact that an occasional weekly sample in some control persons showed large numbers of tetracycline-resistant organisms suggests unrecognized ingestion of a tetracycline, possibly in food, at some time before the sampling.

Previous studies have reported more frequent drug resistance in bacteria isolated from human beings on farms with livestock given antibiotic feed than from those on farms without animals.[22-24] One report matched antibiotic-resistant patterns of *Esch. coli* from farm families with those from their animals.[25] These studies have recorded such differences many years after multiple drug usage on these farms. Our study now records prospectively a change with time in the intestinal flora of farm dwellers as compared with neighbors in the presence of one antibiotic feed and in the known absence of any other antibiotic usage. The change occurred within four to six months after introduction of the feed to the farm and did not occur in the neighbors. This apparent selection for resistant organisms was reversible after nine months' usage of tet-feed on the farm since it was not present six months after removal of the tet-feed from the farm.

The rapid conversion of animal intestinal flora to drug resistance after animal ingestion of antibiotic-supplemented feed has been described.[13,26,27] Such a finding was seen in our studies with tet-feed. The predominant organism, however, remained *Esch. coli* despite the presence originally of 10 to 20 per cent tetracycline-resistant strains of *P. mirabilis*. This observation suggests that *Esch. coli* have a selective advantage in the intestinal tract over *P. mirabilis*. The different antibiotic-resistance patterns of bacteria from the same chickens fed tetracycline inside and outside the barn suggest an environmental influence, as well, on the intestinal flora. All chickens in a cage showed similar intestinal flora, illustrating a communal reservoir of organisms.

Patients being treated with tetracycline were found to excrete fecal coliforms with multiple resistance patterns.[14] In previous farm studies, multiple resistance patterns were found in bacteria isolated from animals, but the use of many drugs could have led to this finding. We have been able to observe prospectively in this natural farm setting the rapid selection by one drug, tetracycline, for resistance to other unrelated antibiotics. After three to four months' exposure to tetracycline on the farm, chickens and human subjects excreted bacteria that were resistant to other antibiotics, but linked with tetracycline on a plasmid. In the chicken, we had detected low numbers of organisms resistant to sulfonamides, tetracycline and streptomycin before introduction of tet-feed. We assume that these organisms were then selected by tet-feed, but we do not know why the multiply resistant organisms should increase in frequency over those with single tetracycline resistance. The origin of resistance to ampicillin-carbenicillin is also unclear. Furthermore, in the chickens, where alimentation could be controlled, we noted more frequent transfer of the tetracycline-resistant gene as the number of resistance patterns in *Esch. coli* increased.

No change in intestinal flora was seen in persons eating eggs from tet-fed chickens. During the time of this study, no sickness occurred that was associated with resistant organisms. However, the resistant intestinal bacteria represent a reservoir of transferable resistance genes. The tetracycline gene is associated with transfer genes on many plasmids, and, in fact, many resistances were transferred linked with resistance to tetracycline. The possible transfer of these plasmids from nonpathogenic to pathogenic bacteria or from animal to man must be considered a potential consequence of increased resistant bacteria in the farm environment.

The rise in frequency of resistant organisms in our environment is the obvious result of antibiotic usage. The only means to curtail this trend is to control the indiscriminate use of these drugs. All areas of antibiotic usage deserve critical evaluation. Contrasting views have been expressed regarding the real as opposed to the potential human health hazard of resistant bacteria in animals and the impact of antibiotic-supplemented feeds on this problem.[1,3,7,27,28] The present findings clearly demonstrate, however, that antibiotic-supplemented feed is a factor contributing to the selection of human resistant strains of bacteria. These data speak strongly against the unqualified and unlimited use of drug feeds in animal husbandry and speak for re-evaluation of this form of widespread treatment of animals.

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R-Factors of *Escherichia coli* from Dressed Beef and Humans[1]

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One hundred eighty *Escherichia coli* strains isolated from raw and cooked dressed beef and from healthy humans were screened for resistance to each of nine antibiotics: chlortetracycline, ampicillin, chloramphenicol, kanamycin, neomycin, nalidixic acid, dihydrostreptomycin, oxytetracycline, and tetracycline. Nearly 80% of the 98 beef isolates and 54% of the 82 human isolates were resistant to one or more of the antibiotics tested. Ampicillin resistance was most frequent among beef isolates, and dihydrostreptomycin resistance was most frequent among isolates of human origin. About 74% of the multiply resistant beef strains and 86% of the multiply resistant human strains transferred all or part of their resistances to *E. coli* K-12 recipients.

Transferable drug resistance, mediated by plasmids called R-factors, was first demonstrated in Japan in 1959 (2). Since then, the occurrence of R-factors has been extensively documented and several reviews have been published (3, 5-8, 11). The demonstration that R-factors from *Escherichia coli* isolated from animals could be transferred to resident *E. coli* in humans (10) has lent support to the idea that R-factor-bearing strains of *E. coli* associated with livestock present a potential hazard to humans. Although *E. coli* strains possessing R-factors have been isolated from sausages (9), little is known about the extent to which *E. coli* strains with R-factors are associated with other meat products.

This study (portion of a thesis presented by the senior author in partial fulfillment of the requirements for the M.S. degree in bacteriology at North Dakota State University) was made to determine the incidence of R-factor-bearing strains of *E. coli* in dressed beef. Additionally, the incidence of R-factor-bearing *E. coli* strains in healthy humans was determined for comparative purposes.

MATERIALS AND METHODS

Bacterial strains. Samples of both raw and cooked dressed beef were obtained from the North Dakota State University Food Service, and fecal swabs were provided by students enrolled in bacteriology courses. Presumptive *E. coli* strains were isolated and identified by routine methods; all isolates exhibited typical *E. coli* characteristics on EMB agar, Kligler iron agar, and Simmons citrate agar. Antibiotic-resistant mutants of *E. coli* K-12 F^- (ATCC 14948) were employed as recipient strains in all conjugation experiments. Mutagenesis was performed either by ultraviolet irradiation or by treatment with *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (K and K Laboratories, Plainview, N.Y.) using the procedure described by Adelberg et al. (1). The mutants, designated *E. coli* K-12 C, *E. coli* K-12 K, and *E. coli* K-12 NE, were resistant to 10 μg of chloramphenicol per ml, 50 μg of kanamycin per ml, and 250 μg of nalidixic acid per ml, respectively.

Media and antibiotics. Bacterial cultures were maintained on brain heart infusion (Difco) agar slants and were routinely grown in trypticase soy broth (TSB, Baltimore Biological Laboratories). Penassay (Difco) agar was used as the base in selective media and in the determination of resistances according to the procedure of Bauer et al. (4). The antibiotics contained in the multitipped disks (Consolidated Laboratories, Inc., Glenwood, Ill.), used for the determination of antibiotic-resistance patterns, were ampicillin (10 μg), chloramphenicol (30 μg), chlortetracycline (30 μg), dihydrostreptomycin (10 μg), kanamycin (30 μg), nalidixic acid (30 μg), neomycin (30 μg), oxytetracycline (30 μg), and tetracycline (30 μg). Ampicillin trihydrate (Parke, Davis, and Co., Detroit, Mich.), chloramphenicol (Sigma Chemical Co., St. Louis, Mo.), kanamycin sulfate (Sigma Chemical Co., St. Louis, Mo.), nalidixic acid (Sigma Chemical Co., St. Louis, Mo.), streptomycin sulfate (Nutritional Biochemicals, Cleveland, Ohio), and tetracycline hydrochloride (The Upjohn Company, Kalamazoo, Mich.) were used in selective media at final concentrations of 10, 10, 30, 100, 10, and 30 μg/ml, respectively.

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Conjugation procedure. Conjugation experiments were performed essentially by the procedure described by Watanabe and Fukasawa (12). Each donor or recipient strain was grown in 10 ml of TSB, with shaking, for 6 hr at 37 C. Then, 1-ml portions of the donor and recipient cultures were mixed in a tube containing 2 ml of TSB. After the conjugation mixture had been incubated at 37 C for 18 hr, samples were plated on selective media containing appropriate combinations of antibiotics. Controls consisted of donor and recipient cultures which were incubated and plated separately. When conjugation was achieved, the antibiotic-resistance patterns of representative recombinants were determined with multitipped disks.

RESULTS AND DISCUSSION

A total of 180 strains of *E. coli* was isolated from dressed beef and humans. Although the frequency of isolates having at least one resistance was higher among the 98 dressed beef isolates (79.6%) than among the 82 human isolates (53.7%), resistant human strains averaged considerably more resistances per organism (3.93) than resistant beef strains (2.28). As many as eight resistances were detected in a single dressed beef isolate, whereas seven resistances were the most exhibited by an individual human isolate.

Table 1 presents the frequencies at which resistance to each of the nine antibiotics occurred. Resistance to ampicillin was most common among beef isolates, whereas this resistance was only the fifth most common among human isolates. Resistance to dihydrostreptomycin, the most common resistance for human isolates, was the second most common among beef strains.

The 11 most frequent of the 21 different resistance patterns exhibited by beef isolates are presented in Table 2. Human isolates had a total of 13 different resistance patterns, and the 8 most frequent are shown in Table 3. A single resistance to ampicillin was, by far, the most frequent resistance pattern among strains from dressed beef. Although nonresistant human isolates were more frequent than human isolates having a particular resistance pattern, a higher percentage of resistant human strains were multiply resistant (88.6%) than were resistant beef strains (53.7%). Resistances to chlortetracycline, oxytetracycline, and tetracycline were usually concurrent.

All resistant isolates were tested for their ability to transfer their resistances to appropriate *E. coli* K-12 F⁻ recipients. In instances where no transfer was initially achieved, possibly because the selected marker was chromosomal, or when all resistances were not transferred, the experiment was repeated using a

TABLE 1. *Frequencies of individual resistances*

Resistance[a]	Beef isolates		Human isolates	
	No. of strains resistant	Percent frequency	No. of strains resistant	Percent frequency
A	14	7.9	34	19.7
AM	60	33.7	18	10.4
C	7	3.9	1	0.6
K	9	5.1	5	2.9
N	7	3.9	5	2.9
NE	8	4.5	3	1.7
S	42	23.6	39	22.5
T	17	9.6	34	19.7
TE	14	7.9	34	19.7

[a] Abbreviations: A, chlortetracycline; AM, ampicillin; C, chloramphenicol; K, kanamycin; N, neomycin; NE, nalidixic acid; S, dihydrostreptomycin; T, oxytetracycline; TE, tetracycline.

TABLE 2. *Eleven most frequent resistance patterns of beef isolates*

Resistance pattern[a]	No. of strains	Percent frequency
AM	29	29.6
None	20	20.4
AM-S	14	14.3
S	7	7.1
A-AM-K-N-S-T-TE	5	5.1
AM-C-S	3	3.1
NE-S	2	2.0
A-T-TE	2	2.0
NE-S-T	2	2.0
A-S-T-TE	2	2.0
A-AM-T-TE	2	2.0

[a] For abbreviations, see footnote to Table 1.

TABLE 3. *Eight most frequent resistance patterns of human isolates*

Resistance pattern[a]	No. of strains	Percent frequency
None	38	46.3
A-S-T-TE	16	19.5
A-AM-S-T-TE	8	9.8
AM-S	4	4.9
S	3	3.7
A-T-TE	3	3.7
A-AM-K-N-S-T-TE	3	3.7
AM	2	2.4

[a] For abbreviations, see footnote to Table 1.

TABLE 4. *Frequencies of transfer for individual resistances*

Resistance[a]	Beef isolates: No. having resistance	Beef isolates: No. transferring resistance (%)	Human isolates: No. having resistance	Human isolates: No. transferring resistance (%)
A	14	7 (50.0)	34	28 (82.4)
AM	60	19 (31.7)	18	10 (55.6)
C	7	3 (42.9)	1	1 (100.0)
K	9	6 (66.7)	5	5 (100.0)
N	7	5 (71.4)	5	5 (100.0)
NE	8	3 (37.5)	3	2 (66.7)
S	42	36 (85.7)	39	35 (89.7)
T	17	8 (47.1)	34	28 (82.4)
TE	14	7 (50.0)	34	28 (82.4)

[a] For abbreviations, see footnote to Table 1.

different recipient strain or selective conditions, or both. By so doing, considerably more resistance transfer was detected. Table 4 indicates the frequencies at which individual resistance determinants were transferred; all were transferable at high frequencies. It should be noted that the conjugal transfer of resistance to nalidixic acid has not been reported previously.

Considering only multiply resistant isolates, 73.8% of those from dressed beef and 84.6% of those from humans were able to transfer all or part of their resistances. Of the beef strains having the most common multiple resistance pattern, "ampicillin-dihydrostreptomycin," 42.9% transferred the resistances completely and 50.0% transferred only resistance to dihydrostreptomycin. The most common resistance pattern of human isolates, "chlortetracycline-dihydrostreptomycin-oxytetracycline-tetracycline," was completely transferred by 93.8% of the isolates having that pattern.

This study has demonstrated a high incidence of transferable antibiotic resistance in *E. coli* strains isolated from dressed beef and healthy humans. If ingested, the R-factor-bearing strains of *E. coli* associated with dressed beef could give rise to serious health problems. However, the *E. coli* strains already present in the humans sampled would seem to be even more potentially harmful because these strains tended to be more multiply resistant and also were capable of transferring their resistances at higher frequencies than could the beef strains.

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Plasmid-Linked Ampicillin Resistance in *Haemophilus influenzae* Type *b*

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Four ampicillin-resistant, β-lactamase-producing strains of *Haemophilus influenzae* type *b* were examined for the presence of plasmid deoxyribonucleic acid (DNA). Three resistant strains contained a 30×10^6-dalton (30 Mdal) plasmid and one resistant strain contained a 3-Mdal plasmid. The ampicillin-sensitive *Haemophilus* strains examined did not contain plasmid DNA. Transformation of a sensitive *H. influenzae* strain to ampicillin resistance with isolated plasmid DNA preparations revealed that the structural gene for β-lactamase resided on both plasmid species. DNA-DNA hybridization studies showed that the 30-Mdal *Haemophilus* plasmid contained the ampicillin translocation DNA segment (TnA) found on some R-factors of enteric origin. The significance of this finding is discussed in relation to the possible origin of the *H. influenzae* plasmids.

Disease due to ampicillin-resistant strains of *Haemophilus influenzae* type *b* has become an increasingly serious and widespread problem (1, 3, 25). Ampicillin-resistant strains have been isolated from cases of epiglottitis, pneumonia, otitis media, and meningitis, including three fatal cases of infant meningitis (15, 17). The primary cause of ampicillin resistance appears to be the production of a β-lactamase shown in one strain to possess a broad-spectrum penicillinase-cephalosporinase activity (9). Thorne and Farrar (J. Infect. Dis., in press) recently have demonstrated transfer of the ampicillin resistance from one strain to an ampicillin-sensitive strain during mixed incubation, presumably by conjugation.

The sudden emergence of ampicillin resistance in *H. influenzae* due to a transferable β-lactamase gene suggested to us, and others (9,15), that an R-factor might be involved. In this study we report the isolation of plasmid deoxyribonucleic acid (DNA) from four ampicillin-resistant strains of *H. influenzae*. Three strains contained a 30×10^6-dalton (30 Mdal) plasmid and one strain contained a 3.0-Mdal plasmid, and evidence is presented indicating that the β-lactamase gene is located on those plasmid species. Resistance to ampicillin mediated by the TEM-type β-lactamase in enteric bacteria is found on a segment of DNA that can be translocated from replicon to replicon (13). This same segment is found on the plasmid DNA isolated from resistant *H. influenzae*.

MATERIALS AND METHODS

Bacterial strains. The strains used in this study and their sources are as follows. *H. influenzae* HR-7 and HR-9, Clyde Thornsberry, Center for Disease Control, Atlanta, Ga.; *H. influenzae* HR-B and G32, Ann Larson, Clinical Microbiology Department, University of Washington, Seattle; *H. influenzae* HR-665, Stephen Cohen, University of California, San Francisco Medical Center; and *Escherichia coli* RS2, Fred Heffron, Department of Microbiology, University of Washington, Seattle.

Media. The liquid medium contained 3.5% brain heart infusion (Difco) supplemented with 10 μg of hemin, 10 μg of L-histidine, and 3 μg of nicotinamide adenine dinucleotide per ml (22). The solid medium (chocolate agar) consisted of GC agar (Difco) containing 2% defibrinated sheep blood heated at approximately 80 C for 10 to 15 min. Cultures on solid media were incubated at 36 C in a CO_2 incubator (CO_2 concentration, 3 to 8%). The ampicillin-resistant strains were grown on chocolate agar supplemented with ampicillin (20 μg/ml). Cultures in broth were grown in a shaking platform air incubator at 36 C.

Assay of β-lactamase activity. β-Lactamase activity was measured by the acidimetric method of Rubin and Smith (21). One unit of β-lactamase activity was defined as the amount of enzyme hydrolyzing 1 μmol of benzyl penicillin in 1 h at 25 C.

Measurement of minimum inhibitory concentration (MIC). The agar dilution method of Steers et al. (24) was used. Inocula were prepared from 4- to 6-h-old broth cultures and diluted to give viable counts of approximately 5×10^5 organisms/ml. A replicator delivering 0.001 ml was used to inoculate the agar surfaces of media containing antibiotics of interest.

Preparation of cell lysates and ultracentrifugation procedures. The bacteria were grown to about 10^9 cells/ml in liquid media. The cells were harvested by centrifugation and lysed by a modification of the method of Clewell and Helinski (2) in which Triton X-100 (0.1% final concentration) was used in place of Brij 58. Covalently closed circular (CCC) plasmid DNA was further purified by isopycnic centrifugation in a CsCl-ethidium bromide gradient as previously described (10). The final density was adjusted to 1.7936 g/cm^3 (refractive index, 1.4080), and the solution was centrifuged for 40 to 48 h at 15 C and 40,000 rpm in a Beckman type 50 rotor.

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DNA bands in the gradients were located by using a black-light lamp (UVL-22, Ultraviolet Products Inc., San Gabriel, Calif.). Chromosomal and plasmid DNA bands were collected from the side of the gradient tube by using an 18-gauge needle and a 3-ml syringe.

DNA contour length. Plasmid DNA was spread onto parlodian-coated electron microscope grids according to the Kleinschmidt method (8). Well-isolated molecules were photographed under the electron microscope, and the developed negatives were projected through a photographic enlarger onto paper and traced. The contour length of the tracing was determined by using a map measurer. The true magnification of the electron microscope was determined by calibration with a diffraction grating, and the molecular weights of the plasmids were calculated by assuming 1 μm of DNA to be equivalent to 2.07 × 10^6 daltons.

Preparation of labeled plasmid DNA. ^{3}H-labeled RSF1030 DNA was prepared from strain 1485 of *E. coli* as previously described by Heffron et al. (13).

Extraction of unlabeled DNA for hybridization. Unlabeled whole-cell DNA from ampicillin-sensitive and -resistant strains of *H. influenzae* was prepared by the method of So et al. (23).

DNA-DNA duplex studies. Labeled and unlabeled DNA were sheared by sonication before hybridization in a Branson sonicator model 140D for 5 min at 4 C (output setting, 3) and then dialyzed against 0.42 M NaCl. Hybridizations were performed as described by Cross et al. (5). Approximately 0.001 μg of ^{3}H-labeled, sheared RSF1030 DNA (specific activity, 1.5 × 10^6 counts/min per μg) was mixed in a glass vial with 150 μg of unlabeled whole-cell DNA in a total volume of 1.5 ml of 0.21 M NaCl. The DNA was allowed to reanneal at 70 C for 125 min. Renaturation was stopped by placing the vials into an ice-cold water bath. The S1 endonuclease reaction was carried out as previously described (5). The actual degree of duplex formation for the homologous reaction was 72 to 78%, whereas the actual degree of duplex formation with the chromosomal control was 5 to 6%. Normalized values (recorded in the table in this paper as percentage of homology) were obtained from raw data by subtracting the chromosomal control and dividing by the homologous reaction.

Transformation. The transformation method used was that basically described by Cohen et al. (4). After the 42 C heat pulse, the transformation mixture was diluted 1:5 into L broth and incubated for 4 h at 37 C to allow phenotypic expression. Cells were then plated on chocolate agar supplemented with 1.0 μg of ampicillin per ml. Plates were then incubated in a CO$_2$ incubator at 36 C for 48 h.

RESULTS

Production of β-lactamase by resistant H. influenzae. The resistant *H. influenzae* strains used in this study were typical type *b* organisms with surprisingly high MICs to ampicillin (Table 1). Since resistances of this magnitude are usually associated with the production of a β-lactamase, we examined sonicates of our resistant *Haemophilus* strains and found that they all possessed enzymatic activity. No β-lactamase activity was detected in the sonicate of the ampicillin-sensitive strain, G32.

The rates of hydrolysis of several β-lactam antibiotics by sonically disrupted cells of *H. influenzae* strain HR-7 and *E. coli* RS2, a strain containing the plasmid R1drd-19, which specifies a TEM-type β-lactamase, are shown in Table 2. The so-called TEM-type β-lactamase exhibits high activity on ampicillin and cephaloridine substrates but low activity against isoxazolyl penicillins such as oxacillin and methicillin (11). The β-lactamase produced by strain HR-7 had high activity on ampicillin and peni-

TABLE 1. *MICs of ampicillin for H. influenzae strains*

Strain no.	MIC (μg/ml)
G32	0.25
HR-7	700
HR-885	>1000
HR-B	20
T7-1[a]	>1000
T7-5[a]	>1000
T8-13[b]	700
T8-2[b]	>1000

[a] Transformant strain derived from the exposure of strain G32 to the plasmid DNA isolated from strain HR-7.

[b] Transformant strain derived from the exposure of strain G32 to the plasmid DNA isolated from strain HR-885.

TABLE 2. *Relative rates of hydrolysis of various β-lactam antibiotics by culture sonic fluids of H. influenzae HR-7 and G32 and E. coli R32*

Sonic fluid	Substrate					
	Penicillin G[a]	Ampicillin	Cephalothin	Oxacillin	Methicillin	Dicloxacillin
HR-7	100 (756)[b]	111	20	13	0	0
RS2	100 (150)	95	17	7	2	2
G32	0	0	—[c]	—	—	—

[a] Penicillin G = 100.

[b] Numbers in parentheses indicate rate of hydrolysis relative to benzyl penicillin (specific activity expressed as units per milligram of bacterial protein).

[c] —, Not done.

cillin G and low activity against oxacillin and methicillin and resembled the general substrate profile of the *Haemophilus* β-lactamase characterized by Farrar and O'Dell (9).

Demonstration of plasmids in resistant H. influenzae. On the basis of its substrate specificity, the β-lactamase found in strain HR-7 appeared analogous to the TEM-type class, the most common R-factor-associated β-lactamase (11). Therefore, we next examined our ampicillin-resistant strains to determine whether they contained plasmid DNA. Cleared cell lysates were prepared and centrifuged in CsCl-ethidium bromide. All of the resistant strains examined contained a DNA component characteristic of circular, covalently closed (CCC) molecules. This DNA component was absent in the ampicillin-sensitive strain, G32 (Fig. 1). Material from the CCC region of the gradients was pooled, extracted with isopropyl alcohol, dialyzed, and allowed to stand at 4 C for 1 week. The DNA molecules were then examined in the electron microscope, and well-isolated, open, circular DNA molecules were photographed and measured (Table 3).

Plasmids of two distinct sizes were seen. Strains HR-7, HR-9, and HR-B contained a plasmid approximately 30×10^6 Mdal in mass (Fig. 2). The plasmid fraction of strain HR-7 also contained a CCC DNA species with a mass of 60 Mdal. This larger plasmid species constituted less than 1% of the total plasmid DNA, and we assume that it represents a dimer of the predominant 30-Mdal plasmid.

Ampicillin-resistant strain HR-885 contained

TABLE 3. *Control length measurements of plasmids from ampicillin-resistant H. influenzae strains*

Strain no.	No. of molecules measured	Mean mol wt
HR-7	30	29.9 ± 0.73
T7-1	28	30.2 ± 0.59
HR-885	22	2.94 ± 0.08
T8-2	36	3.19 ± 0.12

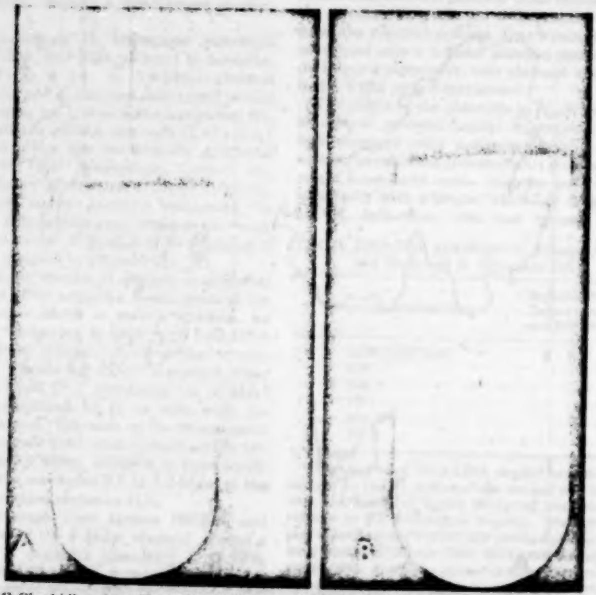

FIG. 1. *CsCl-ethidium bromide gradient tubes containing cleared cell lysates of (A) ampicillin-sensitive H. influenzae strain G32 and (B) ampicillin-resistant H. influenzae strain HR-7.*

a much smaller plasmid with a mass of approximately 3 Mdal (Fig. 2). The presence of some linear DNA in our original plasmid preparations derived from this strain raised the possibility that we were missing a larger plasmid species either by our isolation procedures or by the action of nucleases. Plasmid DNA preparations from strain HR-885, in which meticulous care was taken to avoid chromosomal DNA contamination, contained very little linear DNA, and no plasmids larger than 3 Mdal were seen. We could find no plasmid smaller than 30 Mdal in either the CCC DNA fraction or the chromosomal fraction of the CsCl-ethidium bromide gradients of strain HR-7. In addition, cell lysates of the ampicillin-sensitive strain, G32, were run in CsCl-ethidium bromide gradients and the area of the gradient where CCC normally banded was carefully examined in the electron microscope for circular DNA, but none was found.

Transformation of ampicillin resistance by Haemophilus plasmid DNA. To show definitively that the gene for β-lactamase was located on the *Haemophilus* plasmids, we used plasmid DNA isolated from the resistant strains, HR-7 and HR-885, to transform a sensitive recipient, G32, to ampicillin resistance (Table 4). Chromosomal DNA from these resistant strains lacked transforming ability. Exposure of the sensitive strain, G32, to plasmid DNA isolated from HR-7 and HR-885 resulted in the appearance of a significant number of ampicillin-resistant clones. These transferred clones now showed the same plasmid species as the parental HR-7 and HR-885 strains (Table 3) and also synthesized a potent β-lactamase.

The MICs of the donor strains, recipient strain, and several of the transformant strains are given in Table 1. It is clear that transformant strains may have either higher or lower MICs to ampicillin relative to the donor strain. This might be due to so-called "intrinsic factors," i.e., altered surface properties of recipient bacteria, which have been shown to play an important role in the resistance of gram-nega-

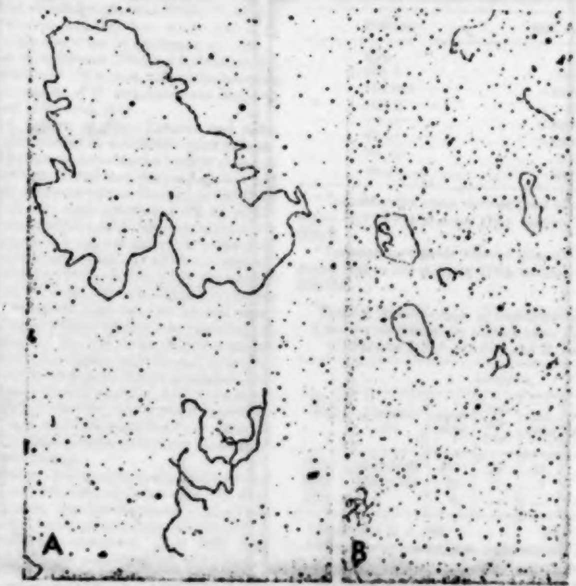

FIG. 2. Electron micrograph of H. influenzae plasmids isolated by dye-buoyant density centrifugation from (A) strain HR-7 and (B) strain HR-885. Final magnification, ×*17,342.*

TABLE 4. *Transforming capacity of plasmid DNA isolated from ampicillin-resistant Haemophilus strains*

Source of transforming DNA	No. of ampicillin-resistant transformants (per 10^8 cells)[a]
HR-885 plasmid DNA	23.1
HR-7 plasmid DNA	3.3
HR-885 chromosomal DNA	0
HR-7 chromosomal DNA	0

[a] Transformations were done according to the method of Cohen et al. (4). After incubation of $CaCl_2$-treated cells with the various DNA preparations (1 μg/ml), bacteria were diluted fivefold into antibiotic-free L broth. After 4 h of incubation at 37 C, samples of the bacterial cultures were spread onto chocolate agar containing ampicillin and incubated for 24 to 48 h for determination of the numbers of transformants. Each value shown is an average of two experiments.

tive bacteria to β-lactam antibiotics (19). Furthermore, it has been shown that the host bacteria cytoplasm may control some R-factor gene functions including β-lactamase production (16).

Hybridization of H. influenzae plasmids with RSF1030. RSF1030 (referred to hereafter as R-AMP) is a 5.5- to 5.6-Mdal plasmid present in its host *E. coli* as a multi-copy pool of about 30 copies per chromosome equivalent (6). R-AMP contains a DNA sequence (TnA) of 2.7 to 3.3 Mdal in size that includes the structural gene for the TEM β-lactamase. Current evidence suggests that a diverse group of R-factors, isolated from enteric bacteria containing the TEM-type β-lactamase gene, arose as the result of the translocation of this 2.7-Mdal sequence of DNA from plasmid to plasmid (12, 13).

To determine whether *H. influenzae* plasmids contained a DNA sequence homologous to the TnA sequences found in enteric bacteria, we hybridized ^3H-labeled R-AMP with cold DNA extracted from selected *Haemophilus* strains (Table 5). Unlabeled DNA extracted from strains HR-7 and T7-1, containing the 30-Mdal plasmid, hybridized to 42 to 48% with the R-AMP plasmid. The size of the homologous region calculated from those hybridization values is 2.3 to 2.6 Mdal, which is in good agreement with the measured 2.7 to 3.3 Mdal of the TnA translocation sequence (13).

DNA extracted from strains HR-885 and T8-8, harboring the 3-Mdal plasmid, shared a lower level of sequence homology, 21 to 26%, with the R-AMP plasmid. In terms of molecular weight the region of homology is 1.2 to 1.4 Mdal in mass, which is close to the estimated mass of the structural gene for β-lactamase, 0.9 Mdal (11). DNA extracted from the ampicillin-sensitive *H. influenzae* strain, G32, shared only 1% of its sequences with R-AMP.

DISCUSSION

Ampicillin has been extensively used to treat *Haemophilus* infections for over 10 years without the appearance of resistant strains. The recent alarming increase in high-level ampicillin resistance among strains of *H. influenzae* type *b* suggested to a number of investigators that genetic elements analogous to the R plasmids of enteric bacteria might be involved. This view was strengthened by the observation that ampicillin resistance in *Haemophilus* was mediated by a β-lactamase. We have now shown by physical and genetic means that this speculation is correct by demonstrating plasmid DNA in ampicillin-resistant *H. influenzae* strains. The majority of the resistant strains we examined contained a 30-Mdal plasmid. Transformation of an ampicillin-sensitive *H. influenzae* strain with isolated plasmid DNA revealed that the structural gene for β-lactamase resided upon the plasmid genome. One strain, HR-885, contained only a 3-Mdal plasmid species. Like its larger counterpart, this plasmid also specified a TEM-type β-lactamase.

The origin of the plasmids in *H. influenzae* is of critical epidemiological importance. If we had observed only a single plasmid species within the resistant *Haemophilus* strains, a case might have been made that we were dealing essentially with a single "clone" of drug-resistant *H. influenzae* that had become widely

TABLE 5. *DNA-DNA hybridizations between RSF1030 and whole-cell H. influenzae DNA*

Source of unlabeled DNA	Relative DNA sequence homology with RSF1030 (%)[a]
C600 (RSF1030)	100
G32	1
HR-7	48
T7-1	42
HR-885	21
T8-8	26

[a] The degree of DNA-DNA duplex formation was assayed by the S1 endonuclease method (5). In every case, the degree of duplex formation was calculated relative to the homologous reaction. The actual extent of binding of [^3H]RSF1030 purified plasmid DNA with whole-cell *E. coli* C600 (RSF1030) was approximately 80%, which was corrected for a 5% reaction between [^3H]RSF1030 DNA and whole-cell DNA extracted from an *E. coli* F^- strain. Each value shown is an average of three reactions.

disseminated throughout the world. The finding of the much smaller HR-885 plasmid indicates that either there have been several independent genetic events leading to the development of resistant *Haemophilus* strains or that a single plasmid has already undergone a series of recombinational interactions. The best clue that we presently have as to the origin of the plasmids of *H. influenzae* comes from two observations. The first is that the 30-Mdal plasmid is conjugative. We have shown that the conjugative *H. influenzae* plasmid described by Thorne and Farrar (J. Infect. Dis., in press) is 30 Mdal in mass (Elwell and Falkow, unpublished observations), whereas Thorne and Farrar (personal communication) have demonstrated that the HR-7 strain examined by us is capable of transferring ampicillin resistance to a *Haemophilus* recipient by conjugation. Not unexpectedly, the HR-885 strain containing the 3-Mdal plasmid was not transmissible by their methods. Hence, at least some of the plasmids found in *Haemophilus* apparently possess a transfer mechanism similar to that found in the R plasmids of enteric bacteria.

The second line of evidence for the origin of the plasmids of *Haemophilus* comes from our demonstration that the segment of DNA containing the structural gene for the TEM β-lactamase in R-factors of enteric origin is similarly found on the plasmids in *Haemophilus*. It is now clear that many of the drug resistance determinants found on R plasmids are carried on DNA sequences capable of being translocated from replicon to replicon (13; Berg and Davies, personal communication). For example, this translocation sequence carrying the TEM β-lactamase gene (TnA) is found on R-factors of enteric origin regardless of their incompatibility class, overall guanine plus cytosine content, strain, or geographical source (13). This observation, taken together with the conjugative nature of the *Haemophilus* plasmid, is consistent with the view that the 30-Mdal plasmid found in *H. influenzae* may have originated from one of the established R-factor incompatibility classes of enteric plasmids. However, our attempts to demonstrate the transfer of the 30-Mdal *Haemophilus* plasmids to *E. coli* K-12 have not been successful, nor have Thorne and Farrar (J. Infect. Dis., in press) been able to demonstrate the conjugal transfer of ampicillin resistance from *Haemophilus* to either *E. coli* or *Klebsiella pneumonia*. Although these observations may be interpreted as evidence against an enteric species as the origin of the plasmids of *Haemophilus*, it is worth noting that several of the R-plasmids of *Pseudomonas aeruginosa* are promiscuously transmitted to a variety of species, including soil saprophytes, *Neisseria perflava*, and photosynthetic bacteria (18), but in some cases are not capable of intergeneric transfer to *E. coli* (14). In addition, the entire plasmid or the Ampicillin translocation sequence may be capable of insertion into the bacterial chromosome (20). Thus, some ampicillin-resistant strains of *H. influenzae* may exist without demonstrable cytoplasmic DNA. This possibility and others are being investigated by means of DNA-DNA heteroduplex analysis.

The 3-Mdal *Haemophilus* plasmid is nontransmissible by conjugation, although it easily transformed ampicillin-sensitive *Haemophilus* strains. This smaller plasmid species appears to contain the equivalent of 1.2 to 1.4 Mdal of the 2.7-Mdal TnA sequence. Perhaps this plasmid is a derivative of the 30-Mdal plasmid, being selected out of its larger progenitor by a series of recombinational events. If this was the case, it argues for a very specific reduction of plasmid DNA that resulted in reduction in size by a factor of 10, leaving the essential plasmid genes and the structural gene for β-lactamase intact. An alternative possibility is that the 30-Mdal plasmid was co-resident in a cell containing a small indigenous plasmid of *Haemophilus* and that a portion of TnA segment was translocated to the indigenous plasmid species. Eventually, the larger plasmid might have been eliminated from its host bacterium, leaving only the small plasmid containing a portion of the TnA translocation sequence. Heteroduplex analysis and further physical characterization of the 30-Mdal plasmid should clarify the question of its origin. In any event, the smaller plasmid is a model of efficiency, capable of replicating itself and specifying a β-lactamase enzyme in the short space of 3 Mdal of DNA.

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Plasmid-Mediated Beta-Lactamase Production in *Neisseria gonorrhoeae*

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Several β-lactamase-producing, penicillin-resistant strains of *Neisseria gonorrhoeae* were examined for R plasmids. Penicillin-resistant strains isolated from men returning from the Far East and their contacts contained a 4.4 × 10^6-dalton plasmid in common. Transformation studies and the isolation of a spontaneous penicillin-susceptible segregant showed that the structural gene for β-lactamase was part of the 4.4 × 10^6-dalton plasmid. An additional penicillin-resistant gonococcal strain isolated in London was found to harbor a 3.2 × 10^6-dalton R plasmid. Deoxyribonucleic acid (DNA)-DNA duplex studies revealed that the penicillin-resistant gonococcal isolates contained a significant portion (about 40%) of the transposable DNA sequence, TnA, which includes the β-lactamase gene commonly found on R plasmids of the *Enterobacteriaceae* and *Haemophilus influenzae*.

It has been known for some time that the R plasmids of enteric species enjoy a very broad host range (1, 14). The recent finding (reviewed in 4, 6, 28) that certain plasmid-mediated antibiotic resistance genes reside upon discrete sequences of deoxyribonucleic acid (DNA) that have the capacity to transpose from plasmid to plasmid has further demonstrated that the range of plasmid-mediated antibiotic resistance genes might be even broader than that of the whole plasmid genome. Therefore, plausible mechanisms exist by which pathogenic microorganisms, previously antibiotic susceptible, may be converted to stable antibiotic resistance by the direct extension of an entire R plasmid or by the simple addition of only a segment of DNA to a preexisting indigenous plasmid gene pool (6, 15, 19).

Previous studies from this laboratory (21) and others (3, 24, 30) have established that most strains of *Neisseria gonorrhoeae* contain plasmid species that are cryptic in the phenotypic sense. For example, our examination of 30 antibiotic-susceptible gonococcal isolates showed that 28 strains harbored a multicopy (2.6 ± 0.2) × 10^6-dalton (2.6 MDal) plasmid, and 1 strain contained a 24.5-MDal plasmid species, whereas 1 strain was plasmid free (13; L. P. Elwell and S. Falkow, *in* R. Roberts, ed., *The Gonococcus*, in press). The demonstration of a widespread plasmid gene pool in gonococci together with the emergence, epidemiology, and molecular nature of R plasmids mediating ampicillin resistance in *Haemophilus influenzae* (11, 12) led us to speculate (15) that gonococci were likely candidates to acquire plasmid-mediated penicillin resistance specified by a β-lactamase. Consequently, the recent isolation of β-lactamase-producing strains of *N. gonorrhoeae* (2, 25, 26) prompted us to examine them for the presence of a novel DNA species that might represent an R plasmid.

In this study we report the detection of plasmid species from three penicillin-resistant clinical isolates of *N. gonorrhoeae*. We further demonstrate that these plasmids probably represent a direct or indirect extension of the plasmid gene pool of enteric species to gonococci.

MATERIALS AND METHODS

Bacterial strains. Penicillin-resistant strains of *N. gonorrhoeae* were kindly supplied by Clyde Thornsberry, Center for Disease Control, Atlanta, Ga. The strains, CDCO1, CDC66, CDC67, and CDC36N, were recent representative isolates from United States military personnel recently returned from the Far East as well as a sexual contact (3, 25). The IPL strain was originally isolated in London from the vagina of a woman with a pelvic inflammatory disease (26). The gonococcal strains F62 and KH45 were antibiotic-susceptible laboratory strains whose plasmid complement have been previously characterized (21; Elwell and Falkow, in press). Penicillinase production of the parental strains as well as selected transformants was detected by using the chromogenic cephalosporin method (23). Resistant strains were maintained on modified Kellogg agar (21) supplemented with 1 μg of penicillin G per ml.

Agarose gel electrophoresis of DNA. Plasmid

DNA was initially detected and characterized by the agarose gel electrophoretic method (22). The strains of *N. gonorrhoeae* were grown overnight in 30 ml of modified GC medium (Difco) supplemented as described by Mayer et al. (21). Cleared lysates were prepared (16, 22) and, after ribonuclease digestion and phenol extraction, the clear aqueous phase was adjusted to 0.2 M sodium acetate (final concentration) and precipitated with ethanol. The precipitate was dissolved in 0.2 ml of TES buffer [50 mM NaCl-5mM ethylenediaminetetraacetic acid (EDTA)-50 mM tris(hydroxymethyl)aminomethane (Tris) (pH 8)] and electrophoresed in a 0.7% agarose gel dissolved in Tris-borate buffer (pH 8.2) (89 mM Tris base-2.5 mM sodium EDTA-89 mM boric acid). DNA was visualized by staining with ethidium bromide and viewing the gel under long-wave ultraviolet light. Plasmid DNA of known molecular weight was included in each gel as a standard (22).

Preparation of plasmid DNA. Unlabeled covalently closed circular (CCC) plasmid DNA was prepared as previously described (19). $[^3H]$thymine-labeled RSF1050 plasmid DNA was prepared from *Escherichia coli* 1485 as described by Heffron et al. (18, 19).

DNA contour length. Plasmid DNA was spread onto parlodion-coated electron microscope grids by the Kleinschmidt technique (10). Molecular weights of the plasmids were calculated as previously described (18, 19).

DNA-DNA hybridization studies. Unlabeled whole-cell DNA from penicillin-resistant and -susceptible strains of *N. gonorrhoeae* was prepared by the method of So et al. (29). For DNA-DNA duplex studies, approximately 0.01 μg of ^3H-labeled, sheared, denatured RSF1050 plasmid DNA was incubated with 150 μg of unlabeled, sheared, denatured DNA from each of the indicated organisms. DNA reassociation was performed in 0.21 M NaCl at 68°C for 240 min. At the end of the incubation period, samples were assayed by the S_1 endonuclease technique (7).

RESULTS

Detection of R plasmid in *N. gonorrhoeae*. Figure 1 shows the agarose gel electrophoresis of ethanol-precipitated plasmid DNA from cleared lysates of selected *N. gonorrhoeae* strains. The prominent band of linear chromosomal DNA migrates to a characteristic position in such gels and may obscure CCC plasmid species of about 10×10^6 to 15×10^6 daltons, depending upon its width (22). Figures 1A and B contain lysates extracted from the antibiotic-susceptible laboratory strains KH45 and F62 and show the presence of previously characterized CCC plasmids of 24.5 and 2.6 MDal, respectively. The faint DNA band in Fig. 1B, appearing between the 2.6-MDal CCC plasmid species and the chromosomal band, represents the open circular (OC) form of the 2.6-MDal plasmid. The identification of this intermediate band as the OC form of the 2.6-MDal plasmid species was deducted from the direct electron microscopic examination of molecules extracted from this band as well as the direct observation of the banding patterns of known 2.6-MDal CCC and OC species (see also 22). Figures 1C and D contain lysates extracted from independently isolated penicillin-resistant strains CDC66 and CDC67 contracted by military personnel in the Far East. The lysate of strain CDC66 (Fig. 1C) shows the CCC and OC forms of the 2.6-MDal indigenous plasmid and an additional plasmid species that migrates in the agarose gel at a position (relative to the molecular weight standard [Fig. 1H]) characteristic of a CCC molecule with a molecular mass of 4.4 MDal. The lysate of strain CDC67 (Fig. 1D) contains both the 2.6- and 24.5-MDal plasmids typical of gonococci, but also contains a 4.4-MDal plasmid species. The association of the 4.4-MDal molecular species with the penicillin-resistant phenotype was materially strengthened by examining the lysate extracted from a penicillin-resistant strain, CDC01 (Fig. 1F), isolated from a case contact and a spontaneous pencillin-susceptible derivative of CDC01 (Fig. 1E). It may be seen that the lysates from these two strains differ in only one aspect, namely, the 4.4-MDal plasmid species.

The lysate extracted from the penicillin-resistant IPL strain isolated in London from a patient with pelvic inflammatory disease is shown in Fig. 1G. The IPL strain was found to contain the 2.6-MDal plasmid and a unique plasmid species that, migrated at a position, relative to the molecular weight standards (Fig. 1H), for a CCC molecule with a molecular mass of 3.2 MDal.

The number and molecular mass of the plasmid species in the gonococcal isolates were verified by isolating purified CCC DNA from each strain and measuring the contour lengths of OC species seen in the electron microscope. The results were in excellent agreement with the agarose gel data. Relative to the indigenous gonococcal plasmid, which was taken as a molecular mass of 2.6 MDal (21, 24, 30), the molecular masses of the unique plasmid species present in the Far East and London strains were calculated to be 4.3 ± 0.15 and 3.2 ± 0.2 MDal, respectively, based on measurements of at least 10 molecules. In subsequent studies we have been able to transform, by using the method of Cohen et al. (5), a suitable *E. coli* recipient to ampicillin resistance (Ap^r) with purified plasmid DNA from the penicillin-resistant strains CDC36N and IPL. The resulting *E. coli* Ap^r transformants derived from CDC36N DNA contained a single plasmid species corresponding

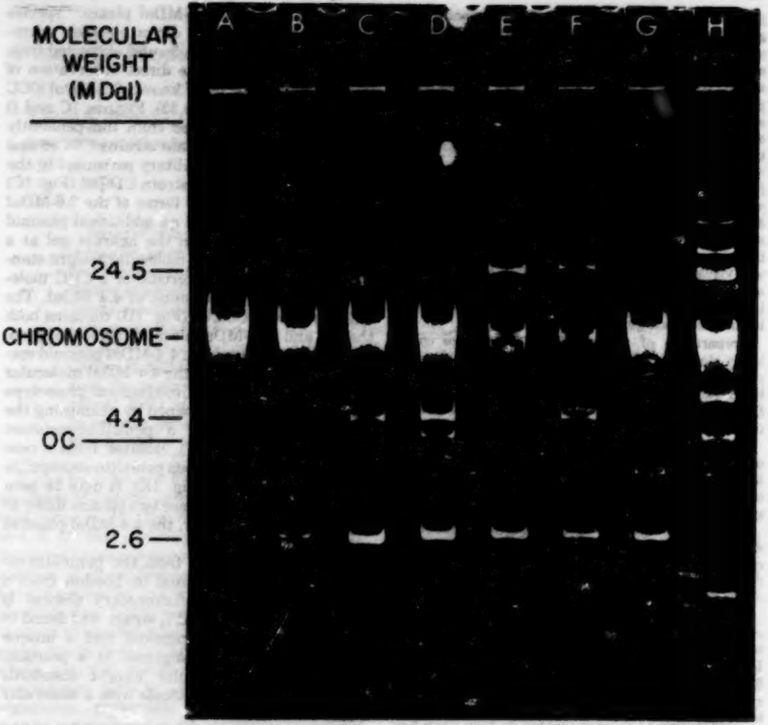

FIG. 1. *Agarose gel electrophoresis of ethanol-precipitated DNA from cleared lysates of penicillin-susceptible (Pen^s) and penicillin-resistant (Pen^r) N. gonorrhoeae strains. (A) Strain KH45 (Pen^s) containing the 24.5 $\times 10^6$-dalton cryptic plasmid; (B) strain F62 (pen^s) containing the 2.6 $\times 10^6$-dalton cryptic plasmid; (C) strain CDC66 (Pen^r), Far East isolate; (D) strain CDC67 (Pen^r), Far East isolate; (E) spontaneous Pen^s derivative of strain CDC01; (F) strain CDC01 (Pen^r), from case contact of patient infected in the Far East; (G) strain IPL (Pen^r), London, England, isolate; (H) standard plasmid DNAs, ranging in size from 62 $\times 10^6$ (uppermost band) to 1.9 $\times 10^6$ daltons (lowest band). OC refers to the open circular form of the 2.6 $\times 10^6$-dalton cryptic plasmid.*

to 4.3 MDal, whereas the *E. coli* Ap^r transformants obtained with IPL DNA contained a single plasmid species of 3.2 MDal. The complete molecular characterization of these plasmids is currently in progress (M. Roberts, L. P. Elwell, and S. Falkow, manuscript in preparation). Nevertheless, the preliminary data presented here provide sufficient evidence to conclude that the penicillin resistance of the Far East and London gonococcal isolates is plasmid mediated.

Origin of β-lactamase genes residing on gonococcal plasmids. Although gonococci relatively resistant to penicillin have been known for a number of years (reviewed in 15), the penicillin-resistant gonococci isolated from the Far East and London were unlike any previously described strains in that they elaborated a β-lactamase that conferred resistance to penicillin, ampicillin, and cephaloridine, similar to the TEM β-lactamase of enteric species (2, 26, C. Thornsberry, personal communication; unpublished data from this laboratory). It is well established that among R plasmids within species of the family *Enterobacteriaceae*, the gene specifying the TEM β-lactamase resides upon a common transposable 3.2×10^6-dalton sequence of DNA (3, 4, 6, 17-19). The ability of this DNA sequence, TnA, to be excised from one plasmid and become inserted into a recipient plasmid has been suggested as an explanation for the ubiquity of the TEM β-lactamase gene among R plasmids of the *Enterobacteriaceae* and other bacterial species (15, 17-19). It seemed of considerable interest, therefore, to determine whether any, or all, of the TnA DNA sequence was present in the penicillin-resistant strains of *N. gonorrhoeae*. To study this possibility, DNA-DNA duplex studies were performed.

Whole-cell DNA was prepared from the *N. gonorrhoeae* Far East isolates CDC66 and CDC67, the London isolate IPL, as well as the laboratory strains F62 and KH45. [^{3}H]thymine-labeled RSF1050, a 4.9-MDal ColE1 plasmid derivative containing the entire TnA sequence (29), was hybridized against the unlabeled gonococcal whole-cell DNA. RSF1050 served as a particularly convenient probe for TnA since this sequence comprised about 50% of the entire plasmid genome (F. Heffron, P. Bedinger, J. Champoux, and S. Falkow, submitted for publication). Table 1 shows the results of the hybridization experiments. Labeled RSF1050 plasmid DNA shared no DNA sequences in common with the drug-susceptible strains of *N. gonorrhoeae* harboring either the 24.5- or 2.6-MDal indigenous plasmids. In contrast, all of the penicillin-resistant strains tested contained DNA that bound 20 to 22% of the RSF1050 nucleotide sequence. As indicated in Table 1, ^{3}H-labeled RSF1050 was hybridized against whole-cell DNA extracted from *H. influenzae* (RSF007). The plasmid RSF007 has previously been shown to contain the entire TnA sequence by heteroduplex analysis (11); therefore, the reaction between RSF1050 and *H. influenzae* (RSF007) was assumed to reflect only TnA-TnA interaction. On the basis of a relative DNA sequence homology of 51% in the case of an R plasmid containing the entire TnA segment, it can be estimated that both the 4.4- and 3.2-MDal gonococcal R plasmids contain 39 to 43% of the TnA sequence. To determine whether the homology shared by RSF1050 and the gonococcal R plasmids was specifically in the TnA segment and not another portion of RSF1050, hybridization experiments were carried out with ^{3}H-labeled PMB8 plasmid DNA. PMB8, which is RSF1050 minus TnA, showed no significant nucleotide base sequence homology with unlabeled DNA derived from the penicillin-resistant *N. gonorrhoeae* isolates. Heteroduplex studies are in progress to substantiate these hybridization data.

TABLE 1. *Hybridization between ^{3}H-labeled RSF1050 plasmid DNA and whole-cell DNA*

Source of unlabeled DNA	Relative DNA sequence homology with ^{3}H-labeled RSF1050 plasmid DNA (%)[a]
E. coli W1485 (RSF1050)	100
H. influenzae (RSF007)	51
N. gonorrhoeae F62 (Pen^s)[b]	1
N. gonorrhoeae 45 (Pen^s)	1
N. gonorrhoeae 67 (Pen^r)	22
N. gonorrhoeae 66 (Pen^r)	20
N. gonorrhoeae IPL (Pen^r)	20

[a] The degree of DNA-DNA duplex formation was assayed by the S1 endonuclease method (7). In every case, the degree of duplex formation was calculated relative to the homologous reaction. The actual extent of binding in the homologous reaction was 75 to 78%. All other reactions were normalized to this value set at 100%. Each value shown is an average of three separate determinations. The RSF007 plasmid resident in *H. influenzae* has been previously shown to contain the entire TnA DNA sequence (11). The reaction between RSF1050 and *H. influenzae* (RSF007) was assumed to reflect only TnA-TnA interaction. The reaction between RSF1050 and the gonococcal isolates was also assumed to reflect only TnA-TnA reaction.

[b] Pen^s, Penicillin susceptible; Pen^r, penicillin resistant.

DISCUSSION

The sudden appearance of plasmid-mediated penicillin resistance among strains of *N. gonorrhoeae* in both the Far East and London bears a striking similarity to the earlier emergence of ampicillin-resistant strains of *H. influenzae* (20). Antibiotic resistance in *Haemophilus* strains has occurred by virtue of several independent events, as evidenced by the characterization of two genetically distinct R plasmids from ampicillin-resistant isolates (11, 12, 15). Similarly, antibiotic resistance in *N. gonorrhoeae* appears to be more complex than merely the dissemination of a single R plasmid-containing strain. This conclusion is suggested by the plasmid pattern observed in the lysates of the Far East strains CDC66 and CDC67 since one harbors the 24.5-MDal indigenous plasmid and the other does not (Fig. 1C and D). Both of these isolates carry the 4.4-MDal R plasmid as well as the 2.6-MDal indigenous plasmid. Furthermore, the IPL strain isolated in London presumably represents a third independent resistant strain. Preliminary auxotyping of selected penicillin-resistant isolates (D. Rose, and M. Roberts, unpublished data) supports the conclusion that many of the strains are unrelated and that resistance has occurred by independent genetic events.

A number of investigators (reviewed in 1, 14, 31) have noted that the R plasmid pool of enteric bacteria has been increasing sharply, particularly over the past decade. As the pool of R plasmid-containing enteric bacteria has increased, so has the possibility that R plasmids might emerge that could better cross biological barriers and so, perhaps, enter bacterial species and genera apparently widely different from their original enterobacterial hosts (1, 31). We believe the emergence of penicillin resistance in gonococci provides yet another example of the direct or indirect extension of the enteric R plasmid pool. The R plasmids specifying β-lactamase characterized in *H. influenzae* were shown to contain, in one case, the entire TnA segment and, in another case, at least one-third of the transposable TnA sequence that is found on a wide variety of enteric R plasmids (11, 12, 15). Similarly, in this study we have shown that R plasmids of gonococci likewise contain a significant portion (about 40%) of the TnA sequence. The possibility that a relationship exists between the emergence of plasmid-mediated resistance in *N. gonorrhoeae* and *H. influenzae* is currently under study. Whatever the relationship, the evidence that both of these formerly antibiotic-susceptible pathogens have been recently penetrated by R plasmids, perhaps of enteric origin, has profound implications. For example, a survey of selected strains of *N. meningitidis* for the presence of extrachromosomal DNA has shown that this bacterial species does not ordinarily contain plasmid DNA (Elwell and Falkow, in press). Since *N. gonorrhoeae* and *N. meningitidis* are known to be closely related, we believe that there is cause for concern that meningococci may soon acquire plasmid-mediated drug resistance.

Whether the plasmids carrying a portion of TnA now residing in *N. gonorrhoeae* were directly acquired from some unknown enteric species by conjugation or whether the R plasmids were, in effect, generated by the translocation of the ubiquitous TnA sequence into resident neisserial plasmid species is not clear from currently available data. The relationship between indigenous gonococcal plasmids and gonococcal R plasmids is currently being investigated. A 4.4-MDal plasmid is probably not self-transmissible (14); however, it may be more than fortuitous that the 24.5-MDal cryptic plasmid co-resides with the R plasmid in three of the seven ampicillin-resistant strains we have examined thus far. This large indigenous plasmid was found in only 1 of over 30 antibiotic-susceptible gonococcal isolates that we had previously examined (Elwell and Falkow, in press), and it is tempting to speculate that this large plasmid is mobilizing the smaller R plasmid during conjugation. This possibility is currently being investigated.

Continued surveillance of resistance in *H. influenzae* has provided suggestive evidence that, after the initial breach of some sort of genetic barrier leading to the emergence of R plasmids bearing ampicillin resistance, there have followed in rapid succession R plasmids specifying resistance to tetracycline (8), kanamycin (9), and linked tetracycline and chloramphenicol resistance (B. Van Klingeren, J. Van Embden, and M. Dessens-Kroon, in press). If we look to the future of antimicrobial therapy of gonococcal infections, the experience with *H. influenzae* provides a disquieting precedent.

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Human Therapeutic and Agricultural Uses of Antibacterial Drugs and Resistance of the Enteric Flora of Humans

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Fecal samples were collected from five groups of people differing in the manner of their exposure to antibacterial drugs. The groups included: (i) people working on farms who were continuously in contact with the predominantly resistant florae of farm animals receiving rations containing antibacterial drugs. (ii) people residing on the same farms with no direct exposure to the farm animals, (iii) people treated with antibacterial drugs, (iv) untreated people residing with treated individuals, and (v) untreated people with no exposure to farm animals or treated individuals. The samples were examined by quantitative plating for proportions of antibiotic-resistant, gram-negative enteric organisms. Individual isolates were also examined for their susceptibility to 11 different antibacterial drugs. The results indicate that enteric florae unexposed directly to the selective effects of antibacterial drugs may be affected by contact with predominantly resistant florae directly exposed to antibacterial drugs.

Antibacterial drugs are widely used for production purposes on livestock and poultry farms. This practice has been questioned because it might create conditions detrimental to animal and human health. It has been established that the enteric florae of farm animals are largely composed of drug-resistant organisms as a result of the continuous exposure to antibacterial agents (5, 7–10). Due to the transmissible nature of drug resistance in gram-negative enteric organisms, it has been postulated that the resident animal flora may comprise a reservoir of resistance for animal and human pathogens.

A central question to an objective assessment of the possible danger to public health posed by the agricultural use of antibacterial drugs is whether or not organisms and/or R factors originating on the farm can become established in the florae of human beings who have consumed food of animal origin. An investigation relating to this question was conducted to determine whether or not enteric florae continuously exposed to antibacterial drugs and composed largely of antibiotic-resistant organisms influenced epidemiologically associated enteric florae unexposed to antibacterial drugs. A previous paper reported the high proportions of antibiotic-resistant, gram-negative enteric organisms in fecal samples from Illinois farm animals given feeds containing antibacterial drugs (7). This paper reports the proportions of resistant organisms in fecal samples from the following: human beings working and residing on some of the same Illinois farms, people recently treated with antibacterial drugs, co-inhabitants of treated individuals, and human beings having no exposure to antibacterial drugs and no known contact with treated individuals or Illinois farm animals.

MATERIALS AND METHODS

Media. MacConkey agar (Difco) was used for the determination of proportions of antibiotic-resistant, gram-negative enteric organisms in fecal samples. EMB agar (Difco) was used for secondary isolation of strains selected from MacConkey agar plates spread with fecal suspensions. Mueller-Hinton agar (BBL) was used for antibacterial drug susceptibility testing. Dilutions of fecal specimens were made in sterile saline (0.85% NaCl). Trypticase soy broth (BBL) was used for all broth cultures. Nutrient agar (Difco) slants were used for isolate storage.

Antibiotics. The following concentrations of antibacterial drugs in MacConkey agar were used: nalidixic acid, 40 µg/ml; oxytetracycline, 20 µg/ml; dihydrostreptomycin, 25 µg/ml; and ampicillin, 50 µg/ml. Concentrations of oxytetracycline, dihydrostreptomycin, and ampicillin were selected to provide the best possible correlations between Kirby-Bauer disk susceptibility tests and growth on agar.

Fecal samples. Ten- to 20-g fecal samples were collected into 40-ml quantities of sterile, pH 7.2, buffered-glycerol-saline solution (7) contained in small glass vials. The samples were sent to the laboratory in double-lined mailing containers.

Quantitation of drug-resistant, gram-negative enteric organisms. The procedure used to determine the relative proportions of oxytetracycline-, dihydrostreptomycin-, or ampicillin-resistant organisms has been described in detail (7). This procedure consisted of plating saline dilutions of a fecal suspension on MacConkey agar and MacConkey agar containing antibiotic. After overnight incubation at 37 C, colony counts were used to determine the total concentration of gram-negative enteric organisms present in the initial sample suspension and the concentrations of organisms resistant to each of the three antibiotics. If organisms resistant to one of the antibiotics could not be detected after plating fewer than 10^6 organisms, results for that antibiotic and sample were excluded.

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Isolation and identification of gram-negative enteric isolates. From one to 10 colonies were obtained from antibiotic-free MacConkey agar plates spread with a fecal suspension of each sample. The selection of individual colonies was based upon easily recognizable differences in colonial morphology and differences in their utilization of lactose. Each colony was streaked on EMB agar. After overnight incubation, a single clone from the EMB agar plate was used to inoculate various biochemical test media and a nutrient agar slant. Inocula of broth cultures for antibacterial drug susceptibility testing were obtained from the nutrient agar slant. Isolates were identified according to the methods of Edwards and Ewing (3).

Antibacterial drug susceptibility testing. Antibacterial drug susceptibility testing was performed using high potency sensitivity disks (BBL) as described by Bauer et al. (1). Isolates with intermediate resistance were considered susceptible for the purposes of this investigation.

Exposure of human beings to antibacterial drugs. Fecal samples were arranged into one of five groups according to the direct or indirect exposure of each person to antibacterial drugs. Group 1 consisted of 22 individuals working on 16 farms utilizing antibacterial drug feed additives. These individuals had direct contact with farm animals and their feces. Samples from farm residents claiming to have occasional direct contact with farm animals were included among group 1 samples. Fourteen of the farms raised swine and two raised beef cattle and calves. Group 2 consisted of 20 individuals residing on 13 farms who had no direct contact with farm animals; 10 of the farms raised swine, two beef cattle and calves, and one poultry. Individuals in this group were infants, elderly persons, and housewives. None of the individuals in groups 1 and 2 had been medicated with antibacterial drugs in the preceding 6 months. Groups 1 and 2 represented 20 farms. Group 3 consisted of people who had received antibacterial medication for the treatment of salmonellosis within 3 weeks of the time the fecal sample was collected. Samples in group 4 were obtained from people who resided in the same homes as those in group 3, but had not received antibacterial medication within 6 months. Group 5 samples were obtained from individuals who had not received any type of medication during the 6 months prior to sample collection and lacked contact with farm animals as well as contact with medicated people.

Statistical analyses of proportions of antibiotic-resistant organisms. To perform statistical analyses, the frequencies of organisms resistant to each antibiotic were converted to natural logarithms, and 20 U was added to each logarithm to convert the negative logarithms to positive values. The transformed values for each human group and each antibiotic were used in an analysis of variance (Student's *t* test with significant F).

RESULTS

Antibacterial drugs used as animal feed additives and for treatment of human salmonellosis. Of the 20 farms studied, 14 used chlortetracycline as feed additive, in addition to penicillin G and a sulfonamide in most cases. One of the 14 farms used tylosin in addition of chlortetracycline, penicillin, and streptomycin. One of the swine farms used a nitrofuran derivative and tylosin in addition to penicillin and streptomycin. Each drug was utilized at concentrations ranging from 50 to 100 g/ton.

The 18 medicated people of group 3 all had salmonellosis, and approximately one-third had been hospitalized. None were hospitalized at the time of sample collection. In a few cases, physicians would not reveal the identity of the specific antibacterial drugs prescribed. Ampicillin was administered in 10 of 14 cases. Two of the individuals treated with ampicillin also received chloramphenicol; another received a triple sulfonamide combination in addition to ampicillin. Tetracyclines were utilized in the remaining four cases, with one individual receiving tetracycline in combination with a sulfonamide effective in the intestinal tract and neomycin. Ten of the 18 treated individuals were not receiving antibacterial drugs at the time of sample collection.

Proportions of the gram-negative enteric flora resistant to antibiotics. Fecal samples from the five groups of individuals were examined for the proportions of the gram-negative enteric flora resistant to each of three antibiotics: oxytetracycline, dihydrostreptomycin, and ampicillin. The results of quantitating the proportions of oxytetracycline-resistant organisms are shown in Table 1.

The results are presented as the cumulative percentages of samples which contained equal to or greater than specific numbers of antibiotic-resistant organisms per 100,000 colony-forming units (CFU). In Table 1, the cumulative distributions of samples from groups 1, 2, and 3 were similar. Greater percentages of group 1, 2, and 3 samples contained higher proportions of oxytetracycline-resistant organisms: between 50 and 62% of the samples from groups 1, 2, and 3 contained 10,000 or more oxytetracycline-resistant organisms per 100,000

TABLE 1. *Cumulative distributions of fecal samples from human groups according to proportions of oxytetracycline-resistant organisms*

Determinants	Samples^a (cumulative %)				
	Group 1	Group 2	Group 3	Group 4	Group 5
Resistant organisms per 100,000 CFU					
100,000	0	5	6	3	0
≥10,000	62	50	56	37	13
≥1,000	76	85	78	58	31
≥100	86	90	78	68	41
≥10	91	100	89	76	56
≥1	95	100	95	79	63
Samples with less than 1 resistant organism per 100,000 CFU	5	0	5	21	37
Total no. of samples	21	20	18	38	32

^{a} Groups as described in the text.

CFU. Group 4 samples less frequently contained higher proportions of oxytetracycline-resistant organisms: 37% contained 10,000 or more oxytetracycline-resistant organisms per 100,000 CFU, and 21% contained less than one oxytetracycline-resistant organism per 100,000 CFU. Group 5 samples were least likely to contain resistant organisms: 13% contained 10,000 or more oxytetracycline-resistant organisms and 37% contained less than one oxytetracycline-resistant organism per 100,000 CFU.

Statistical analysis of these results revealed the following: the frequency of oxytetracycline-resistant organisms in group 5 samples was significantly lower ($P < 0.05$) than the frequencies of each of the first four groups. Concomitantly, comparisons among groups 1 through 4 for prevalence of oxytetracycline resistance yielded no statistically significant differences.

The intergroup relationships for proportions of dihydrostreptomycin resistance observed in Table 2 were similar to those observed for oxytetracycline resistance in Table 1. Between 53 and 59% of the samples from groups 1, 2, and 3 contained greater than 10,000 dihydrostreptomycin-resistant organisms per 100,000 CFU. Samples from group 5 infrequently contained high proportions of dihydrostreptomycin-resistant organisms, whereas samples from group 4 generally demonstrated proportions of dihydrostreptomycin-resistant organisms intermediate between those of groups 3 and 5.

Statistical analysis of the frequencies of dihydrostreptomycin-resistant organisms of each group again revealed significantly lower ($P < 0.05$) frequencies in samples from group 5 than in samples from groups 1 through 4. There were no statistically significant differences in frequencies of dihydrostreptomycin-resistant organisms among groups 1 through 4.

The distributions of samples according to proportions of ampicillin-resistant organisms are presented in Table 3. The intergroup relationships found in determinations of proportions of

TABLE 2. *Cumulative distributions of fecal samples from human groups according to proportions of dihydrostreptomycin-resistant organisms*

Determinants	Samples^a (cumulative %)				
	Group 1	Group 2	Group 3	Group 4	Group 5
Resistant organisms per 100,000 CFU					
100,000	5	16	0	3	0
≥10,000	59	58	53	38	10
≥1,000	68	63	71	62	28
≥100	82	84	71	73	34
≥10	95	90	76	78	45
≥1	95	100	88	84	65
Samples with less than 1 resistant organism per 100,000 CFU	5	0	12	16	35
Total no. of samples	22	19	17	37	29

^{a} Groups as described in the text.

TABLE 3. *Cumulative distributions of fecal samples from human groups according to proportions of ampicillin-resistant organisms*

Determinants	Samples^a (cumulative %)				
	Group 1	Group 2	Group 3	Group 4	Group 5
Resistant organisms per 100,000 CFU					
100,000	0	6	7	0	0
≥10,000	67	47	33	23	0
≥1,000	72	65	47	40	14
≥100	86	82	47	53	22
≥10	91	94	53	60	36
≥1	91	100	80	70	61
Samples with less than 1 resistant organism per 100,000 CFU	9	0	20	30	39
Total no. of samples	21	17	15	30	28

^{a} Groups as described in the text.

ampicillin-resistant organisms were similar to those found in determinations of proportions resistant to oxytetracycline or dihydrostreptomycin. Although 20%, or three, of the group 3 samples contained less than one ampicillin-resistant organism per 100,000 CFU, these samples were obtained from three of the four persons who were not treated with ampicillin, but received a tetracycline.

Statistically significant differences ($P < 0.05$) in frequencies of ampicillin-resistant organisms occurred between group 5 and groups 1, 2, and 4. Although significant statistical difference was established between group 4 and group 5, no significant difference in the frequencies of ampicillin-resistant organisms occurred between group 3 and group 5. The distributions of frequencies in groups 3 and 4 were almost identical; however, there were too few samples in group 3, which limited the degrees of freedom, to demonstrate any statistically significant difference between group 3 and group 5. No significant differences occurred when frequencies of ampicillin-resistant organisms from groups 2, 3, and 4 were compared. Frequencies from group 1 were significantly higher than those from the other groups with the exception of group 2.

Antibacterial drug resistances. Table 4 presents *Escherichia coli* susceptibilities to 11 different antibacterial drugs. The occurrence of resistance to nalidixic acid, colistin, nitrofurantoin, chloramphenicol, and gentamicin was uniformly low. Oxytetracycline, dihydrostreptomycin, and ampicillin resistance occurred most frequently among *E. coli* from samples of groups 1, 2, and 3. The frequency of resistance to these three drugs was lowest for samples from group 4 (22% oxytetracycline, 19% dihydrostreptomycin, and 10% ampicillin) and occurred slightly more frequently among *E. coli* from group 5 than group 4. Thirty-three percent of the group 5 isolates were resistant to oxytetracycline, 28% to dihydrostreptomycin, and 13% to ampicillin.

Resistance to neomycin was highest in *E. coli* from groups 1, 2, and 3, ranging between 12 and 19% of the isolates. Resistance to neomycin was absent among *E. coli* of group 5 and was minimal among *E. coli* of group 4. Cephalothin resistance occurred infrequently among *E. coli* from samples of groups 1, 2, 4, and 5, whereas 21% of the *E. coli* from group 3 were resistant to cephalothin. Resistance to sulfamethazine occurred in 51% of the *E. coli* of group 1 and 42% of the *E. coli* from group 2. Resistance to sulfamethazine among *E. coli* from the remaining three groups was lower, ranging between 10 and 16% of the isolates.

Table 5 presents the susceptibilities of all gram-negative enteric isolates to various antibacterial drugs. Resistance to nalidixic acid, colistin, chloramphenicol, and gentamicin was uniformly low for isolates from all five groups. The frequencies of resistance to oxytetracycline and dihydrostreptomycin were similar for isolates from groups 1, 2, and 3, ranging between 33 and 49%. The frequency of oxytetracycline- and dihydrostreptomycin-resistant isolates

TABLE 4. *Antimicrobial drug resistances of E. coli from human groups with varying exposure to the selective effects of antibacterial drugs*

Antibacterial drugs	Isolates resistant to each antibacterial drug (%)				
	Group 1	Group 2	Group 3	Group 4	Group 5
Nalidixic acid	0	4	7	0	0
Oxytetracycline	49	62	50	22	33
Dihydrostreptomycin	60	53	43	19	28
Ampicillin	33	28	37	10	13
Colistin	0	5	0	0	4
Neomycin	12	19	17	1	0
Nitrofurantoin	4	2	0	1	4
Chloramphenicol	0	2	0	0	0
Gentamicin	0	0	0	0	0
Cephalothin	4	0	21	2	5
Sulfamethazine	51	42	14	16	10
Total no. of isolates	57	53	30	117	40

TABLE 5. *Antibacterial drug resistance of all gram-negative enteric isolates from human groups with varying exposure to the selective effects of antibacterial drugs*

Antibacterial drugs	Isolates resistant to each antibacterial drug (%)				
	Group 1	Group 2	Group 3	Group 4	Group 5
Nalidixic acid	1	3	3	3	0
Oxytetracycline	35	49	35	18	24
Dihydrostreptomycin	43	41	33	20	19
Ampicillin	42	36	53	42	24
Colistin	2	3	0	5	2
Neomycin	8	13	6	5	0
Nitrofurantoin	4	3	12	6	3
Chloramphenicol	0	3	0	3	0
Gentamicin	0	0	0	0	0
Cephalothin	19	8	68	43	11
Sulfamethazine	43	41	7	9	10
Total no. of isolates	86	76	87	225	62

from groups 4 and 5 were lower than for groups 1, 2, and 3, ranging between 18 and 24%.

Ampicillin resistance was most frequent (53%) among isolates from group 3 and was least frequent (23%) among isolates from group 5. Similar frequencies (36 to 42%) of ampicillin-resistant organisms were found in groups 1, 2, and 4. Cephalothin resistance was most frequent among isolates of group 3 (68%) and less frequent among isolates from group 4 (43%). Cephalothin resistance was least frequent among isolates from groups 1, 2, and 5. Neomycin resistance was absent among isolates of group 5 and ranged from 5 to 13% in the remaining groups. Sulfamethazine resistance was the most frequent for groups 1 and 2 (43 and 41%) as compared to the resistance for the remaining three groups (between 7 and 10%).

DISCUSSION

Samples from persons recently treated with antibacterial drugs (group 3) and samples from persons working and/or living on farms (groups 1 and 2) contained the highest proportions of gram-negative enteric organisms resistant to oxytetracycline, dihydrostreptomycin, and ampicillin. Resistance to these antibiotics was also most frequent among *E. coli* and all gram-negative enteric isolates from groups 1, 2, and 3. Had all samples of group 3 been obtained from persons receiving medication at the time of sample collection, higher frequencies and a greater prevalence of resistance among isolates of group 3 might have been found.

The presence of ampicillin-resistant organisms in farm animals (7) was reflected in the appearance of ampicillin-resistant organisms in the farm worker and resident. Although ampicillin was not used on the farm, the use of other antibacterial drugs in animal feed appeared to result in the emergence of ampicillin-resistant organisms (7). Kerrebijn et al. (4) noted that the human use of azidocillin, an antibiotic which is similar to penicillin G in its low activity against gram-negative enteric organisms, was associated with an increased prevalence of ampicillin resistance; it was suggested that exposure of organisms to the 6-aminopenicillanic acid nucleus, which is present in all penicillin antibiotics including azidocillin, was responsible for the emergence of ampicillin resistance. Penicillin G was commonly used on the farm.

Group 5 fecal samples contained the lowest proportions of antibiotic-resistant organisms. The proportions of resistant organisms in samples from group 4 were intermediate between the higher proportions observed for group 3 and the relatively lower proportions seen for samples from group 5. The prevalence of resistance to specific antibacterial agents among *E. coli* and all gram-negative enteric isolates from groups 4 and 5 was lower than that of the first three groups. Although ampicillin and cephalothin resistance was less frequent among all gram-negative enteric organisms from group 5 compared to group 4, the absence of differences in the prevalence of resistance in all other instances between the two groups may be accounted for by the limited number of isolates examined.

Cephalothin resistance appeared most frequently in isolates from group 3 and less frequently in isolates from group 4. Some of the β-lactamases produced by gram-negative enterics are active against both ampicillin and cephalosporins and consequently confer cross-resistance to these agents (6). Ampicillin was the most commonly used antibacterial drug in group 3 persons. It is speculated that the activity of ampicillin against gram-negative enterics and the occurrence of cross-resistance between ampicillin and cephalosporins might account for the increased prevalence of cephalothin resistance in groups 3 and 4. The absence of the same degree of activity of penicillin G on gram-negative enterics could explain the lower prevalence of resistance to cephalothin in groups 1 and 2 and the farm animals (7).

The use of sulfonamides on the farm was reflected in a higher prevalence of sulfamethazine resistance in *E. coli* and all gram-negative enteric organisms from groups 1 and 2. The occasional therapeutic use of neomycin in farm animals and its use with group 3 humans was reflected in a slightly increased prevalence of neomycin resistance among isolates from groups 1, 2, and 3.

In this study, no attempts were made to control accidental inhalation or ingestion of drug-supplemented animal feed or to determine whether such inhalation could influence the prevalence of resistant organisms in the flora of the farmer. The highest concentration of any single antibacterial drug in animal feeds in the study was 100 g/ton. The most commonly used combination contained 100 g of chlortetracycline per ton, 100 g of sulfamethazine per ton, and 50 g of penicillin G per ton. Substantial amounts of feed thus would have to be continuously inhaled or ingested to maintain fecal drug concentrations necessary to exert selective effects on the fecal flora of the farmer.

The enteric florae of human beings in contact with farm animals or medicated people contain greater frequencies of resistant organisms than do florae of people unexposed to farm animals or medicated people. Assuming that the direct effects of drugs in feed upon the florae of farm workers and/or residents was minimal, the observations made in this study support the contention that the exposure of one enteric flora to antibacterial drugs, and the consequent emergence of resistant organisms, may alter the composition of epidemiologically adjacent enteric florae unexposed to antibacterial drugs.

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July 8, 1980

The Honorable John Dingell
The House of Representatives
Washington, D.C. 20515

Dear Mr. Dingell:

In connection with the legislation that you and Representative Henry A. Waxman recently introduced into the House of Representatives directing the Food and Drug Administration to remove from use as feed additives antibiotics used in human medicine, I would like to offer the following supporting comments.

As you know, the use of antibiotics in feeds has been steadily increasing since its introduction nearly 30 years ago. This pattern of usage has approximately paralleled that in human medicine and I believe that at present about 50% of all the antibiotics produced in this country are used directly as sub-therapeutic additives to livestock feeds. This usage of antibiotics both in medicine and in agriculture has dramatically altered the environment to which bacteria had ordinarily been exposed during the past and it has evoked a response that is, to say the least, dramatic. Unlike higher species, bacteria are very adaptable and have evolved unique mechanisms whereby different species and even members of entirely unrelated genera are able to exchange special genetic elements known as plasmids and transposons. The precise history of these genetic elements before the era of antibiotics is unknown as they have been discovered and studied only in the recent past. What is very clear, however, is that plasmids and transposons are now ubiquitous and that they frequently contain genes for resistance to antibiotics; moreover, their prevalence may be viewed as the general evolutionary response of the bacteria to the massive dissemination of these substances in agriculture and in human medicine.

Not only are the plasmids and transposons highly mobile but they are also highly plastic - that is they undergo a wide variety of structural rearrangements whereby they acquire new genes and rearrange old ones so as to optimize their genetic content to suit the current environment. Thus, whereas in the early days following their discovery, plasmids usually contained genes for resistance to one or a few different antibiotics, it is now commonplace to encounter single plasmids carrying genes for resistance to as many as 12 different antibiotics at once. A common mechanism for the acquisition of new resistance genes by individual plasmids is through the insertion of transposons. Once assembled, the plasmid containing these several resistance genes is transferred *en bloc* to other bacteria, either related or unrelated, and the presence of any one of the 12 antibiotics will enable those bacteria containing the plasmid to survive and to become resistant simultaneously to the other 11 drugs. In addition, a variety of genes that are involved in the causation of disease by bacteria have recently been found to be located on plasmids; such plasmids are of the same general types that carry resistance genes and in at least one group of bacteria, *E. coli*, the same plasmid has been found to contain genes for antibiotic resistance *and* for pathogenicity. In this case, exposure to one of the antibiotics results in a direct increase in the population of disease-causing bacteria.

From an ecological standpoint, there is universal agreement that the feeding of antibiotics to livestock at doses that are regarded as subtherapeutic brings about the very rapid conversion of the coliform flora from sensitive to totally resistant and similar results have been obtained experimentally with human subjects. Preliminary results of a study currently being conducted under a Food and Drug Administration Contract, in my laboratory and in collaboration with Dr. Gary Dunny of Cornell University School of Veterinary medicine suggest that the same phenomenon occurs with staphylococci and fecal streptococci in pigs (although the conversion of the former is somewhat slower as their natural site is the skin and nasopharynx rather than the GI tract).

Other studies in my laboratory have shown that naturally-occurring bacteria isolated from soil that has been taken from feedlots where animals fed tetracycline have been maintained are much more frequently resistant to tetracycline than bacteria of the same species isolated from feedlots where the animals have not been fed antibiotics. The implication of this result is that antibiotic feeding is responsible for the development of resistance among environmental bacteria as well as among those indigenous to livestock. We suppose that these two types of bacteria interact; the overall evolutionary trend is therefore toward the general increase of bacterial resistance throughout the environment.

It has also been demonstrated repeatedly that multi-resistant coliform organisms and enteric pathogens such as *Salmonellae* are excreted in massive numbers by the animals and contaminate not only various environmental sites such as soil and water but also the meat of the animals that is sold to consumers. Moreover, resistant organisms from livestock fed subtherapeutic antibiotics can sometimes be recovered from the stools of individuals who work closely with the animals and from consumers of the meat of these animals. And it has been established clearly that the same resistance-carrying plasmids can be isolated from bacteria causing disease in man as from those present in the feces and in the meat of livestock fed antibiotics.

It should also be noted that antibiotic treatment of bacterial diseases both in humans and in livestock has been steadily losing effectiveness over the years due to the emergence of resistance and that a variety of human pathogens, some causing serious diseases have only recently and for the first time acquired resistance-bearing plasmids that have interfered with treatment, often with fatal consequences.

A difficult question for which there is at present no precise answer is that of the precise magnitude of the contribution of resistant bacteria from livestock to the overall worldwide pool of resistant bacteria and to the incidence of therapeutic compromise in man due to antibiotic resistant bacteria. The major single disaster that has occurred as a consequence of wholesale antibiotic feeding was the well-known paratyphoid epidemic that occurred in Great Britain during the 1960's and led that country to institute veterinary control over the dispensing of antibiotics. It is, however, noteworthy that several Western European countries have recently instituted prohibitions similar to those proposed and I am not aware of any adverse consequences to date, either with respect to meat prices or to the meat industry in general.

Nevertheless, the overall state of affairs is clearly sufficient grounds for regarding the overuse of antibiotics as a hazard and for clearly differentiating antibiotics into those used in human medicine and those used for livestock. This differentiation should include, incidentally, a prohibition for use in livestock of any antibiotic that results in an increased survival of bacteria resistant to any antibiotic used in human medicine even if the one in question is not so used. An example would be tylosin, an antibiotic that is not to my knowledge used in human medicine but one whose use selects for resistance to all of the group of antibiotics known as macrolides, some of which, such as erythromycin, are very important in human medicine.

I would suggest also that the distinction between "therapeutic" and "subtherapeutic" levels of antibiotic dosage is entirely artificial. At least one group of veal calves has recently been rejected in its entirety by the USDA because the animals contained so much tetracycline that their bones were yellow, even though they were fed tetracycline for "subtherapeutic" purposes.

Passage of the law proposed by Representatives Waxman and Dingell would effectively remove the hazard to human health that results from the feeding to livestock of antibiotics that are used in medicine. Possibly the bacteria indigenous to livestock would become resistant to the substitute antibiotics that would have to be used but they would not become resistant to antibiotics that are used to treat human disease and so could no longer be responsible for therapeutic compromise in humans. A number of substitute antibiotics are already available and others could soon be developed that adequately serve the needs of the livestock industry and will remove from consideration the question of human health hazards.

I would like to add, although it may not be directly relevant to the passage of your bill, that the question of efficacy ought also to be considered.

Industry spokesmen frequently assert that antibiotics would not be used if they were not effective and that their effectiveness has continued undiminished during the nearly thirty years that they have been in use as additives. Both of these assertions are simply untrue. Most of the favorable experimental data are from the early fifties, studies done in recent years very frequently show seriously diminished effectiveness, ineffectiveness, or even a detrimental effect of antibiotic feeding on the wellbeing of the animals. And it is also true that many meat producers function very effectively without using antibiotics at all. However, it is important to realize that the current habits of antibiotic usage developed during an era in which resistance had not yet become a serious problem; it is unfortunate that ingrained habits are difficult to change even in the face of clear evidence that they are dangerous; any number of examples could be cited - an obvious one is that of cigarette smoking - therefore it is very unlikely that habits of antibiotic use will change spontaneously even though it has become clear that the practice of feeding antibiotics is not only hazardous to human health, but also is much less effective, both for growth promotion and for disease prophylaxis than it was at the outset; in my view, a strong case could be made for sharply restricting the use of even those antibiotics that are not used for humans.

Sincerely yours,

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RN/lk

THE DEVELOPMENT AND SPREAD OF ANTIBIOTIC RESISTANT BACTERIA AS A CONSEQUENCE OF FEEDING ANTIBIOTICS TO LIVESTOCK

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BACKGROUND

In the early 1950's it was discovered that the addition of relatively low doses of streptomycin or tetracycline to the feed of chicks resulted in a substantial growth advantage over chicks that had not been so treated. This finding was soon extended to other animals and over the years has grown into a major industry. At present, something close to 50% of all the antibiotics produced in the U.S. is added directly to the feed of farm animals, chiefly poultry, pigs and beef cattle.

Although the initial purpose was to obtain the so-called "growth promotion" effect, there has also developed a very strong feeling among the producers of antibiotics and at least some of the meat producers that the addition of antibiotics to feeds (in somewhat higher doses) produces an important prophylactic effect with respect to bacterial pathogens that may infect the animals. In fact, at present, it is often stated that the use of antibiotics in this manner has made possible the mass production systems (referred to euphemistically by the industry as "intensive animal husbandry") that are in wide use today in the production of meat, poultry, and eggs.

The main problem with these practices is that they always cause the emergence and spread of vast populations of bacteria that are resistant simultaneously to many antibiotics. Curiously, this resistance extends to drugs to which the animals and their bacteria have never been exposed. The reason for this is that the antibiotic resistance genes are carried by plasmids; as individual plasmids often contain genes for resistance to different antibiotics, the use of any one of the drugs for which a plasmid carries resistance will select for the entire plasmid as a "package". As these plasmids can be transferred among bacteria of the same or of different species, and even among species of different genera and families, the hazard becomes more or less universal for animals as well as for humans, rather like the ripples spreading in a pond after a stone has been tossed.

The reason why this situation is still controversial is that it is extremely difficult to obtain direct proof that specific resistant bacteria selected by antibiotic feeding, were transferred from specific animals to specific humans where they were the cause of untreatable disease. Almost all of the available evidence is epidemiological and therefore, in a sense, circumstantial. While it is generally acknowledged that the worldwide overuse of antibiotics is responsible for the problem of widespread and increasing resistance among the bacteria and for the spread of this resistance to new species of pathogens, it is extremely difficult to obtain any reliable quantitative estimate of the relative contributions of human medicine and animal husbandry to this situation.

The growth promotion effect of antibiotics is a phenomenon of some considerable biological interest in that it is clear that the feeding of these substances to young animals results in a greater weight gain per unit of feed and in a more rapid overal growth rate. This effect is almost certainly due to the effects of the drugs on some component(s) of the normal bacterial flora as it does not occur in germ-free animals. Beyond that, however, there is very little definite knowledge, and it is somewhat disturbing, in view of the health hazard for humans that the practice creates, that there is very little interest by the meat producing industry, and still less by the antibiotic producers in finding out precisely what is the mechanism. In fact, to quote Willard Viseck, Professor, Clinical Sciences (Nutrition) at the University of Illinois in this context:

"If you can't pitch it with a fork or spread it on a field, we don't want to know about it". And as for the industry, it should be pointed out that the effect was initially discovered when Stokstad & Jukes (1950) had the bright idea of feeding the chicks the exhausted culture mash from the industrial production of chlortetracycline after the extraction of all of the drug that could profitably be obtained. The resulting growth promotion effect was soon traced to the residuum of antibiotic that was present, and a waste product was converted overnight into a multi-million dollar bonanza for the drug companies, chiefly American Cyanamid (Lederle) and Charles Pfizer & Sons.

As will be seen, antibiotic prophylaxis is very probably useful under certain strictly limited conditions - such as for a very short time during weaning, and at the time of shipping the animals for slaughter. During these times, the animals seem to be especially susceptible to certain bacterial epidemics and, *if they have not been maintained previously on antibiotics*, may derive substantial prophylactic benefits. The problem stems from the fact that the meat producers tend to give antibiotics throughout the entire life of the animal with the consequence that the normal (and abnormal) bacterial flora becomes highly resistant to many antibiotics simultaneously so that the benefits of the drugs at times of stress are drastically reduced.

This paper, then, is an evaluation of the health hazard that is posed by the transfer to humans of bacterial pathogens (and non-pathogens) that are highly resistant to antibiotics as a consequence of the feeding of antibiotics to animals. The conclusions that have been reached on the this analysis are:

(i) Multiply antibiotic resistant coliforms, enteric pathogens, staphylococci and other organisms are widely prevalent in the environment and in the florae of farm animals and man as a consequence of massive antibiotic usage in animal husbandry and human medicine.

(ii) Although there may be minor differences between "animal" and "human" strains for some species, these present little if any barrier to the free transfer of multiply resistant bacterial organisms from animals to man via direct contact, via the environment, and via the food chain.

(iii) These multiply resistant organisms interact with man either by direct colonization, by clinical infection, or by transferring R-plasmids to the human flora and so constitute a substantial hazard to human health due to therapeutic compromise.

(iv) In several cases, resistance genes have been found genetically linked to plasmids that are themselves directly responsible for pathogenicity or for ability to colonize. Here, antibiotic feeding is directly responsible for an increase in human disease.

INTRODUCTION

In 1972, the U.S. Food and Drug Administration spelled out certain criteria that were to be used during a series of experiments intended to evaluate this health hazard (FDA Task Force Report on Antibiotics in Animal Feeds, 1972).

Although these criteria referred primarily to enteric organisms, specifically Escherichia coli and its relatives, especially the Salmonellae, certain other organisms must also be considered. These are organisms that are resident in and often pathogenic for farm animals, can acquire R plasmids, and can infect humans. Some of these, notably the staphylococci, can also colonize without necessarily causing clinical infection.

In Table 1 is a list of microbial pathogens (excluding viruses) that are common to man and domestic animals. Many of these species have plasmid-mediated antibiotic resistance and the species are grouped on the basis of their ability to exchange plasmids. Available information in this connection suggests that the gram-negative bacteria share broadly a large collection of plasmids and that within this group there are wide variations in host specificity, transfer frequency, etc. For the gram-positive organisms, there is presently very little information, but the general impression is beginning to emerge that the situation will be similar to that with the gram-negatives.

Among the species listed in Table 1 are three of the most important bacterial pathogens in the United States, namely, *E. coli*, *Salmonella*, and *S. aureus*. The only one of these for which there is even an estimated frequency of disease in man is the *Salmonellae*, which are thought to cause two to two and a half million clinically significant infections per year (CDC Annual Report, 1977). The others are, if anything, even more common causes of human disease.

For example, *E. coli* is well known to be the commonest cause of urinary tract infection in man, and may still be the commonest cause of other extra-intestinal gram-negative infections. These are not to be taken lightly; a certain proportion of lower urinary tract infections leads to chronic pyelonephritis, a disease that carries a severe morbidity and can be fatal in the long run. *E. coli* septicemia is an extremely serious condition, carrying a case fatality rate of 30% to 50% (Finland and Barnes, 1974). In this condition, effective antibiotic therapy may often make the difference between life and death.

Inasmuch as the problem of antibiotic resistance and its relationship to the use of antibiotics in animal feeds involves primarily these three groups of organisms, the main emphasis will be on them. In the discussion that follows, we shall show: (1) for these three groups of organisms the animal and human populations are either indistinguishable or else widely overlapping; (2) transmission from animals to man has been unequivocally demonstrated for all three groups both in field experiments and by careful epidemiological investigation; (3) for the *Salmonellae*, animals and their products constitute by far the most important source of human infection; and (4) plasmids controlling antibiotic resistance in gram-negative pathogens from animals are indistinguishable from those of gram-negative pathogens isolated from humans; the transfer of such plasmids from animals to man via bacterial colonization has been demonstrated unequivocally.

The discussion will be arranged in three sections as follows:

1. The relationship between strains of various species isolated from animals and humans.
2. Epidemiology of bacterial pathogens common to man and animals.
3. Antibiotic resistant organisms and their conjugative R plasmids.

It must be noted at the outset that there is a vast body of data that, taken as a whole, demonstrates beyond any reasonable doubt that subtherapeutic antibiotic feeding to livestock promotes the emergence and maintains the prevalence of multiply resistant coliforms and Salmonellae and that these spread in large numbers to human populations, so constituting a substantial hazard to human health. These data have been carefully and thoroughly reviewed in two documents, namely the Human Health Appendix (B) of the 1972 FDA Task Force Report on antibiotics in animal feeds, and the Discussion by the Director of the Bureau of Veterinary Medicine of the proposed rulemaking by the FDA on penicillin, published in the Federal Register for August 30, 1977, part IV, and in other sections of this report. This documentation will not be reiterated at full length in this paper. What I shall do instead is concentrate on those points that I feel need to be covered in more detail and on a number of additional organisms and areas that I feel are also deserving of concern in this context.

TABLE 1.

Microbial Pathogens (excluding viruses) Common to Man and Domestic Animals

Species	Pathogenicity Man	Pathogenicity Food Animals	Transmission from food animals to man	Antibiotic resistance plasmids
Escherichia coli[1]	+	+	+	+
Enteric disease-producing E. coli	+	+	2	+
Shigella sp.[1]	+	+	+	+
Salmonella sp.[1]	+	+	+	+
Pseudomonas sp.	+	+		+
Klebsiella - Aerogenes group	+	+		+
Yersinia enterocolitica	+	+	+	+
Yersinia pseudotuberculosis	+	+	+	
Brucella sp.	+	+	+	
Pasteurella multocida	+	+	+	+
Listeria	+	+	+	
Erysipelothrix	+	+	+	
Bacillus anthracis	+	+	+	
Mycobacteria	+	+	+	
Leptospira sp.	+	+	+	
Staphylococcus aureus	+	+	+	+
Streptococcus agalactiae	+	+		+
Bacillus anthracis	+	+	+	
Clostridium perfringens[1]	+	+	+[3]	+
Chlamydia psittacii[1]	+	+	+	+
Mycoplasma sp.	+	+		(+)

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[1] Organisms where all four criteria listed have been documented.

[2] No evidence that strains of E. coli that produce enteric disease in animals cause similar disease in man. However, there is every reason to suppose that enteric

(continued on p. 5)

(footnotes to Table 1 - continued)

disease-producing animal strains are no different from others in their ability to colonize the human G. I. tract. In fact, it is very likely that _E_. _coli_ from animals can transfer / Enterotoxin (Ent) plasmids, especially if associated with antibiotic resistance (Gyles, Palchaudhuri & Maas, 1977) to endogenous human strains with the appropriate K antigen (Ørskov & Ørskov, 1966) or can acquire the appropriate K antigen from endogenous human strains and so become able to cause enteric disease in man. Presumably other virulence factors (see page 36) such as those involved in extra-intestinal infections, can also be transferred.

[g] Animals have not been directly implicated as a source of _C_. _perfringens_ causing human disease.

[h] Antibiotic resistance (to tetracycline) has been encountered; there is no evidence as yet that plasmids are involved (Page, 1977).

1. The existence of overlapping pools of bacterial strain types for species common to man and animals.

Much attention has been given to the question of whether there are discrete bacterial variants or subspecies that are specific for particular animal species. Experimental studies in this area have taken two forms: (i) Can strains isolated from one animal species be differentiated by various cultural and serological characteristics from strains isolated from the same or other species? (ii) Can strains isolated from one animal species colonize or infect others?

(a) *E. coli*

(i) Biology of cross- and superinfection.

Biologically, the relationship between commensal bacteria such as *E. coli* and their animal hosts is extremely complex (Smith, 1975), and I believe it is fair to say that in no case are the various factors involved fully or even well understood. Therefore, even in the few cases where it can be shown that strains isolated from one animal species are demonstrably different from strains of the same bacterial species isolated from another, the true biological significance of these differences with regard to the specificity or stability of adaptations to a given host is far from clear. Similarly, the results of cross-colonization or infection tests, especially negative results, must be interpreted very tentatively and with great caution. In general, the ecological niche comprising the mammalian large intestine or skin or nasopharynx will be occupied by bacteria that are relatively well adapted not only to the species of animal, but also to the particular individual. These organisms form an effective barrier to the establishment of superinfecting variants of the same and sometimes also of different species (Hentges, 1976), so that in this sense, *E. coli* may be regarded as having relatively low *communicability*. Thus, unless the challenging organism is at least as well adapted as the resident or unless the latter are placed at a selective disadvantage - such as by the use of an antibiotic - the challenging organism is unlikely to become established *regardless of its source*. Because of the importance of this situation, it would seem worthwhile to explore in more depth the question of the bio-ecology of *E. coli* with respect to establishment and colonization.

At the outset, it should be remembered that in the usual studies of coliform flora, one does not normally score any strain that makes up less than 1% of the total unless a selective marker is available. This is because of an inherent limitation in the laboratory procedure; it is impractical to score more than about 100 colonies from a single sample. If the total coliform population is 10^9/gm, then strains will be missed if they are present at 10^7/gram or less - a very considerable population size. Because of this practical limitation, colonization is often equated with *predominance* rather than *presence*- an equation that can be misleading.

(1) Composition of the intestinal coliform flora is highly variable with respect to serotype (Richmond/ 1975; Petrocheilou et al., 1976; 1977; Smith, 1969). In some people there is rapid turnover of various serotypes during time periods measured in days or weeks. In others, there is a relatively stable composition of intestinal flora during a time period measured in months. In still others, the flora may be relatively constant during one period, then turn over rapidly during another period. Not surprisingly, the same is true of animals. The most extensive recent studies in this area have been done by the University of Bristol group (Linton, Richmond and coworkers). These

studies have revealed dramatic fluctuations in the composition of the coliform flora during periods of time measured in days in chickens (Howe, Linton and Osborne, 1976a), calves (Howe, Linton and Osborne, 1976b; Howe and Linton, 1976), and pigs (Linton, Handley and Osborne, 1977). This situation is dramatically illustrated in Figure 1. Similar but less detailed results have been obtained repeatedly during the past twenty-five years. A variety of factors may be involved in these shifting patterns: (i) intrinsic individual differences in the colonic environment (Richmond, 1975); (ii) variations in the colonic environment due to diet, digestive activity, antibiotics, and a variety of other undefined physiological factors; (iii) variations in the numbers and properties of new coliform organisms entering the system.

(2) There is great variability among strains in their ability to colonize the colon of various species, of various individuals of the same species, and even in the ability to colonize the same individual from which they were isolated some time previously. It seems probable that there are many variables involved in this situation, for example, dosage, composition of the resident flora, physiological state of the individual including gastric acid content, diet, genetic and physiological adaptivity of the strain, and the presence of phages, bacteriocins and other entities that may interact directly with the bacteria.

(3) The introduction of antibiotics and resistance will result in selection by the antibiotic of a resistant strain (assuming that the resident flora is sensitive), even one that was not well adapted and without the antibiotic would not be able to colonize. In that case, upon withdrawal of the antibiotic, the resistant strain would be lost. Continuation of the antibiotic would maintain selection. Eventually, conditions are likely to change so that the strain becomes

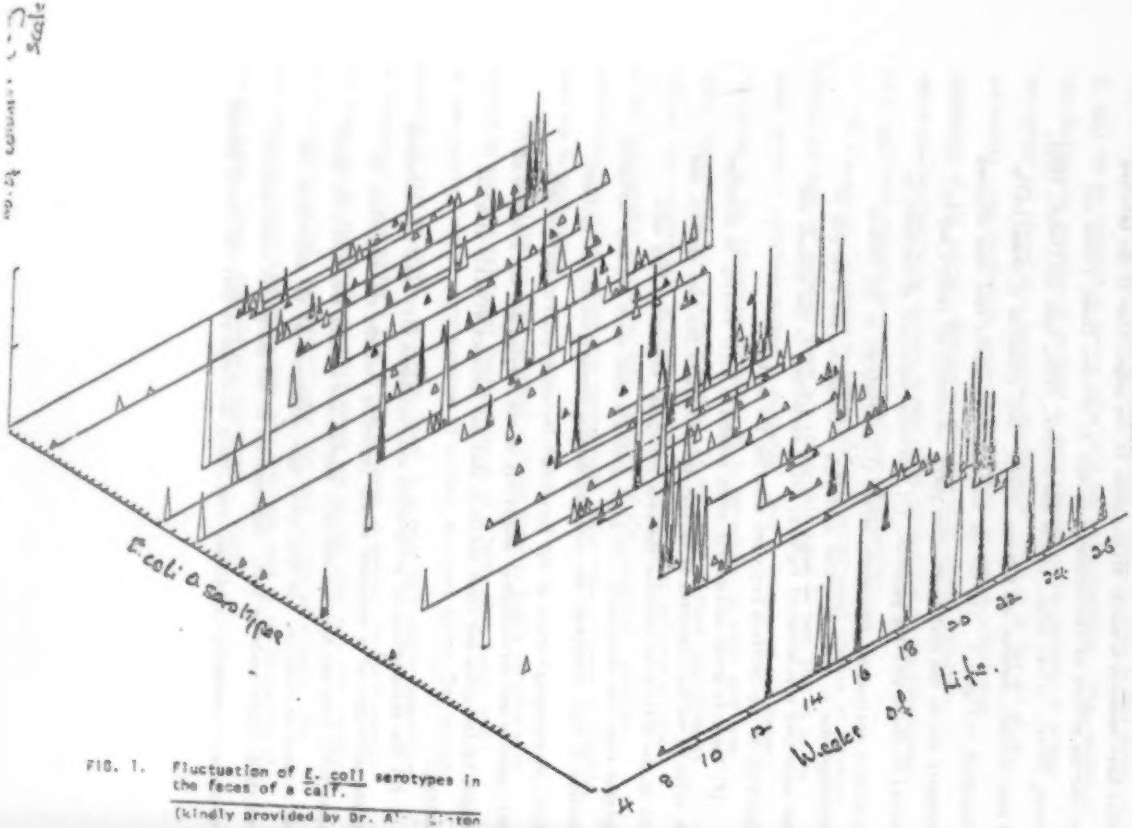

FIG. 1. Fluctuation of E. coli serotypes in the faces of a calf.

(kindly provided by Dr. A[illegible] [illegible]ton better adapted. These changes could involve the colonic environment, which might become more favorable for one or more of the reasons mentioned above, or could involve the microorganism itself, which might undergo genotypic or phenotypic changes making it more adaptive to that particular colonic environment. Alternatively, the resistance determinant might be transferred to a resident strain that was more adaptive to begin with. At this point, *withdrawal of the antibiotic would not result in rapid loss of the resistant strain*. If colonic conditions remained favorable and the flora stable, it might persist for many months or years. If the flora were unstable and turning over rapidly, it would inevitably be lost just as any other strain would be lost *regardless of how adaptive it might have been*. Since the floral composition is generally inconstant, over a long period of time (see Fig. 1) (Levy et al., 1976a; Langlois et al., 1975; Linton, Handley and Osborne, 1977), the resistant strain, or for that matter, any other strain, is very unlikely to persist indefinitely. That is, in the absence of specific selection or reinfection, *any* strain of *E. coli*, resistant or sensitive, is unlikely to persist indefinitely in the colon of any individual.

An unknown in this argument is the role of introduction of new organisms on the colonic flora. It seems probable that this is an important factor, and that both the number and the variety of entering organisms are important; if continual ingestion of a variety of environmental strains or recycling of endogenous strains is occurring, then sooner or later a well-adapted new strain will enter the system, possibly becoming the predominant organism. If these environmental or recycled strains are resistant, then obviously the flora will remain resistant; if they are sensitive, then any resistant organisms present will eventually be eliminated.

While the foregoing argument is hypothetical with regard to mechanism, it should be viewed in the light of the fact that elimination of antibiotics from animal feeds no longer leads to a rapid return to sensitivity of the fecal coliform flora. Farms that have maintained antibiotic-free herds for several years have found that a high percentage of the fecal coliforms are still multiply resistant. Thus, the coliform flora of the pigs studied by Langlois et al. (1975) remained highly resistant in the absence of antibiotics for at least two years. Similarly, the calves studied by Hirsh and Wiger (1975) had a highly resistant coliform flora in the absence as well as in the presence of antibiotics.

Similarly in man, resistant E. coli strains persist in some cases for many months in the absence of antibiotic selection (Hartley and Richmond, 1975). In other cases, such persistence is relatively short-lived. In all probability, however, sufficient numbers of R^+ bacteria survive in the absence of selection to provide a reservoir of these organisms that is always within call, as it were. The level of organisms in this reservoir is assuredly and dramatically increased by the feeding of antibiotics to animals at all dose levels above a certain threshhold as described elsewhere in this report.

(ii) Serotype analyses and their significance.

Although it is often stated that human and animal serotypes of E. coli are distinct, in fact the situation appears rather more complex than that. Among the other possible variables that are rarely considered but may be quite important are local geographic variations in strain distribution (Gruneberg and Bettelheim, 1969). The primary differentiation of E. coli variants is based on serotypes involving O, H, and K antigens. Many studies have demonstrated that some O and O:H serotypes are common to man and domestic animals (Bettelheim et al., 1976;

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Howe and Linton, 1976; Howe et al., 1976c; Hartley et al., 1975), others are more frequently found in animals (Bettelheim et al., 1973), and still others in man (Bettelheim et al., 1973; Howe and Linton, 1976; Hartley et al., 1975). With respect to serotypes, therefore, there are at least grossly overlapping populations, and with respect to antibiotic resistance, an extensive survey by Linton (1977) has shown that the commonest antibiotic resistant serotypes isolated from humans are among the commonest isolated from animals. The results of this survey (Table 2) are reproduced here.

The question of serotypic relationships is compounded by two additional factors that make a definitive evaluation of the significance of serotypes difficult: (i) At least one of the type-specific antignes, the K antigen, is commonly plasmid-linked and consequently is readily transferable between strains (Ørskov and Ørskov, 1966; Smith and Linggood, 1972). (ii) O serotypes are often distinguished by minor biochemical differences in the structure of the cell envelope and consequently may be interconvertible by relatively minor genetic changes, such as mutation, lysogenization, etc. Therefore, even if it were true that a particular envelope structure (as manifested by serotype) contributed substantially to adaptivity to a particular animal host, genetic variants might occur at a sufficiently high frequency to result in relatively common change of host specificity.

For the reasons described above, cross colonization tests carried out in the laboratory do not provide very much more in the way of enlightenment, especially when the results are negative. While it may be true that an E. coli isolate from one animal species is somewhat less likely to be able to colonize a different species than another individual from the same species, this is no more than a broad statistical observation; many isolates from farm animals are

TABLE 2*

Relative incidence of resistant *E. coli* O-serotypes in 3 animal species compared with man

*	Pigs	Poultry	Calves	Man†	*	Pigs	Poultry	Calves	Man†	*	Pigs	Poultry	Calves	Man†
1	+	++	+	4·7	45		++	+		103		++	+	1·2
2	+++	++	++	5·8	46		+			104	+	+		
3	+	++	+		49	+	+			105		+		
4		+	+	1·2	50			+	1·2	106		+		1·2
5	+	+++	+	4·7	51		+++		1·2	107	+++	+	+	1·2
6		+	+	5·8	54		+			108		+	+	1·2
7	++	+++	+	3·5	55				1·2	109	+++	+	+	2·3
8	+++	+++	+++	16·3	57				1·2	110		+	+	
9	+++	+++	+++	18·6	61				1·2	111			+	
10	+				63		+		1·2	112ab		+		
11	+	++	++	2·3	64	++	+		2·3	112ac	+	+		
12			+	1·2	65	+	+			113		+	+	1·2
13	++	+++	+		68		+	+	1·2	114		+	+	
14		+			69	+	++			115		+		1·2
15	++	++	+	1·2	70		+			116				1·2
16	+	++	+	2·3	71	+	+		1·2	117			+	
17		++	+++	1·2	73			+		118	+	+	+	
18			+	4·7	75		+	+	2·3	119		++		
19	+	+		2·3	76			+	1·2	120	+	+++		
19ab	++				77		++	+	5·8	121		+		
20		+++	+	8·1	78	++	+	+	1·2	123		+	+++	2·3
21	+	+++	+++	4·7	79		+			124		+		
22					80		++	+		125			+	
23		+++		3·5	81	+++	+		2·3	126			+	
25		+++	+	7·0	82		+		1·2	127			+	
26	++	+	+++		83	+++			5·8	128		+	++	
27		+		3·5	84	++	+	+		130				5·8
28				1·2	85		++		1·2	131		++	+	2·3
29		+			86		+++	+++	7·0	132	+	+	+	1·2
30	+	+		1·2	88	+	++	+	1·2	133		++		
32			+		89		+		2·3	134	++	++		2·3
34		+++	+		90			+		135		+		
35				1·2	91	+	+++			138	+	+		
36			+		93		++			140	+	+		1·2
37		+		1·2	95	+	+		1·2	141		+		
38		+			96		+++			143	+			
39		+		1·2	98	+				145		+	+	
40	+	++	+		99		+	+	1·2	149	+++	++		1·2
41		+			100	++				150				1·2
42				1·2	101	+++	+	++	10·5	153	+++	+	+	
44			+		102	++	++							

+ = <2%: ++ = 2 – <5%: +++ = 5% and over.

* = O-serotypes.
† = data obtained by different technique (%).

*Linton, A.H. Animal to man transmission of enterobacteriaceae.
Royal Society of Health Journal, June 1977 (Table VI)

as able or even more able to colonize humans than the average human isolate (e.g., Smith, 1969; Smith and Huggins, 1976; Cooke et al., 1972). In fact, it is clear that there is a series of adaptive variations that are either already present or can occur with some frequency permitting colonization of individuals by a strain from another of the same or of a different species. A particularly striking example of this is colicin V (see below, p. 36), a conjugative plasmid-coded substance that increases dramatically the ability of E. coli strains to colonize the mammalian large intestine regardless of their species of origin.

In farm animals as well as in man, as noted above, there is considerable variation among individuals with respect to the composition and stability of the intestinal coliform flora. Thus, attempts to demonstrate colonization may fail for a large variety of reasons, including insensitivity of the testing procedure, only one of which is possible species specificity (Howe and Linton, 1976; Howe et al., 1976a; Linton et al., 1977a). In any case, both cross-colonization tests and biological, especially serotypic, characterizations generally show extensively overlapping sets of animal and human organisms (Linton et al., 1977a,b; Howe et al., 1976b), and there is no biological basis for the concept of stably differentiated species specificity among strains of E. coli.

(b) Salmonella

The general identity of species and strains causing human infections with those that constitute the animal reservoir is very well known. In fact, it is very probable that virtually all Salmonellae of farm animal origin are capable of infecting humans. A single specific serotype, namely S. typhimurium, is by far the most common cause of salmonellosis both in animals and in man (Smith, 1970; Knothe, 1971; CDC 1973 Salmonella Surveillance Summary Report; Anderson, 1968a); moreover, certain other serotypes are very commonly isolated from both man and animals. For example, in the CDC 1974 Annual Salmonella Surveillance, it is reported that six of the most common human serotypes were among the ten most common animal serotypes (CDC, 1974). Similar results have been reported for European isolates (Skovgard and Nielsen, 1972). Even granted that there are some biotypes that are more commonly isolated from chickens, others from pigs, etc., most or all strains and serotypes can cause illness both in man and in farm animals.

(c) Staphylococcus aureus

It is frequently stated that there are species-specific biotypes of S. aureus, and this supposition has proceeded to the extent of defining subspecies such as S. aureus var. Bovis, S. aureus var. Canis, S. aureus var. Hominis. However, the taxonomic criteria, primarily phage typing, serotyping, and nutritional requirements, are somewhat variable. There is considerable overlap, there are biotypes common to two or more species, and cross-colonization and infection between species is quite common. It is particularly instructive that although there is, for example, a fairly well defined bovine biotype, humans are readily colonized by this biotype, and conversely, cattle are readily colonized by human strains (Wallace et al., 1962). Even more instructive is the finding that humans in close contact with cattle as well as cattle in close contact with humans often carry S. aureus strains that have biotypes that are intermediate between those normally considered bovine and human, respectively (Thawley et al., 1977). Thus, although the biotype might be some reflection of adaptive variation among the bacteria, it appears that this presents little or no impediment to cross-colonization and that the adaptive variation may be occurring by either genotypic or phenotypic changes after the organism has become established in a new host. Consequently, with staphylococci as well as with coliforms, it is very doubtful that there are stable species-specific biotypes that are unable to cross-colonize or able to do so only poorly. This situation has been reviewed at length by Live (1972).

(d) Other organisms

Many other microorganisms exist that can be regarded as commensals with man and with farm animals (other gram-negative bacilli, micrococci, streptococci, a variety of anaerobic species, etc.), and many of these are at least opportunistic pathogens. However, there is at present insufficient information on any of them with regard to antibiotic resistance, plasmids, and animal to man transfer, to warrant detailed discussion here. Suffice it to say that these organisms should be looked into; one should not be surprised to find additional pools of overlapping species that carry R plasmids as a consequence of antibiotic feeding and that may add to the potential hazard engendered by these plasmids.

2. *Epidemiology of bacterial pathogens common to man and animals.*

Primary concern in the present context is with the coliforms, including *Salmonellae* and *Shigellae*, and the staphylococci. Both groups of organisms have as their primary reservoir the bodies of living mammals, including man. Both coliforms and staphylococci are normal inhabitants of the mammalian body, the former residing chiefly in the large intestine, the latter in the nasopharynx and on the skin. Although the relationship between bacteria and host is generally stable, it is nevertheless somewhat tenuous; the bacteria may attack their host with consequences of varying severity. Because of the universal occurrence of these organisms in association with mammals, even a very low *frequency* of significant infection results in a tremendous *number* of afflicted individuals. Consequently, *E. coli* and *S. aureus* are among the most frequent cause of bacterial infections, at least in man. *Salmonellae* and *Shigellae* do not differ qualitatively from *E. coli* in that they may also be carried as commensals for many years without causing overt infection; however, the ingestion of a given number of *Salmonella* or *Shigella* organisms is very much more likely to result in overt illness than the ingestion of a similar number of *E. coli* (with the exception of enterotoxigenic or invasive strains of the latter). The majority of infections by any of these organisms (with the exception of *Salmonella typhi*, which is not really under consideration here since it is not ordinarily acquired by man from animals) are benign and self-limited and should not, in general, be treated with antibiotics. Therefore, it is in the majority of cases of little or no *direct* consequence for the afflicted individual whether or not the organisms are resistant to antibiotics. However, all of these organisms have the capacity to cause devastating and sometimes fatal illness. Although the probability of this is much greater in the very young, the very old and in those with reduced resistance, it does occur in normal, healthy adults. In all such cases, of course, antibiotic therapy often means the difference between life and death and so, consequently, does antibiotic resistance among the organisms. Moreover, organisms of relatively low pathogenicity can transfer their R plasmids to others of greater human pathogenicity, and so even if the former were absolutely incapable of causing significant human disease, there would still be a problem.

(a) Salmonellae

The most thorough epidemiological information exists for Salmonellae. The epidemiology of salmonellosis is extremely complicated (Anderson, 1968) and is summarized in the accompanying diagram (Fig. 2). The primary reservoir of Salmonellae is farm animals (Lee, 1974; Anderson, 1968), and other vertebrates including domestic pets such as cats, dogs, turtles (Lamm et al., 1972), and frogs (Bartlett et al., 1977). Among these animals are both clinically ill individuals and asymptomatic carriers, of which the latter as well as the former excrete organisms. Both clinically ill and subclinically infected individuals (animals and human) may become chronic carriers. The frequency of this in animals is very difficult to assess; laboratory experiments give widely variable rates and field surveys are difficult to interpret because feedstuffs are so commonly contaminated with Salmonellae that frequent or even continual reinfection may often be the rule. In swine, for example, various field surveys have detected Salmonella excretion in anywhere from 10% to 85% of healthy animals (Chow et al., 1977; Kobland et al., 1976), and Salmonellae can commonly be isolated from the enteric lymph nodes and other organs as well as from the feces of animals at slaughter (Chow et al., 1977; Groves et al., 1970; Hinton and Williams, 1977; Pennington et al., 1968; Lee, 1974).

The administration of antibiotics is well known to promote the establishment

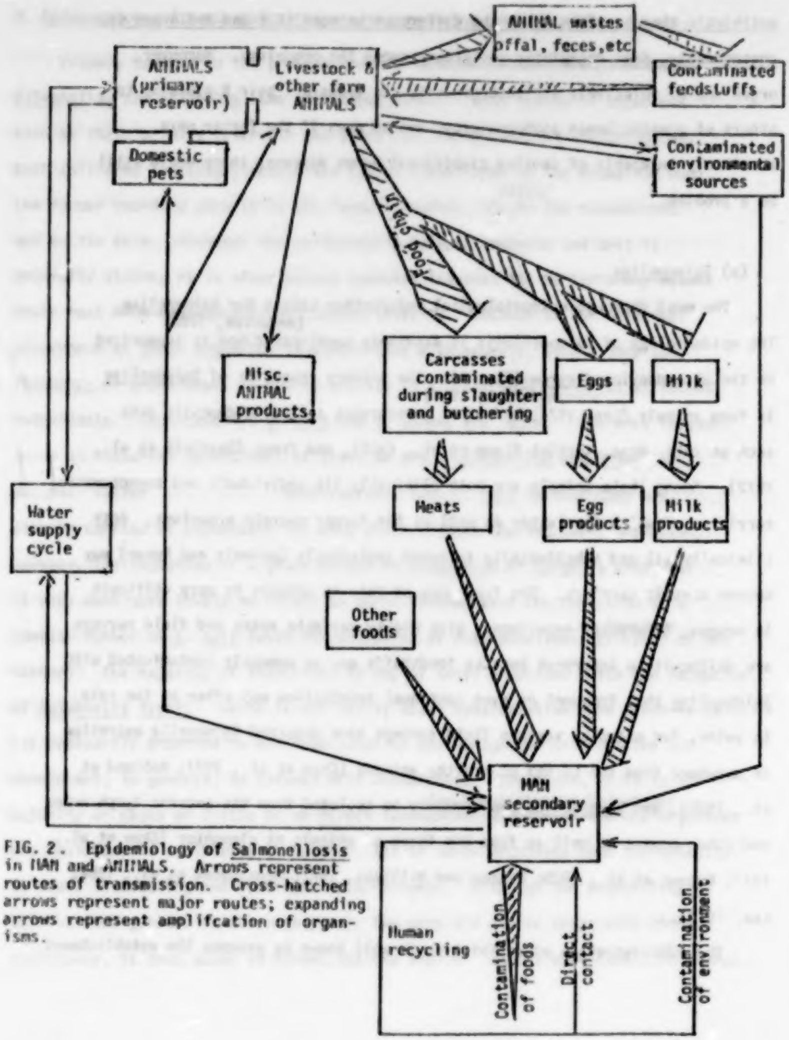
ANIMAL wastes offal, feces,etc
ANIMALS (primary reservoir)
Livestock & other farm ANIMALS
Contaminated feedstuffs
Domestic pets
Contaminated environmental sources
food chain
Misc. ANIMAL products
Carcasses contaminated during slaughter and butchering
Eggs
Milk
Water supply cycle
Meats
Egg products
Milk products
Other foods
MAN secondary reservoir
Human recycling
Contamination of foods
Direct contact
Contamination of environment

FIG. 2. Epidemiology of Salmonellosis in MAN and ANIMALS. Arrows represent routes of transmission. Cross-hatched arrows represent major routes; expanding arrows represent amplification of organisms.

in humans of chronic salmonella carriage (Aserkoff and Bennett, 1969; Hirsh et al., 1973), and it has been demonstrated repeatedly in humans and in animals that antibiotics not only fail to eradicate the organisms even when the latter are sensitive (Aserkoff and Bennett, 1969), but also facilitate the acquisition of sensitive as well as of resistant organisms (Adler et al., 1970). Although the administration of antibiotics to carriers of sensitive _Salmonellae_ results in suppression of the excretion of organisms, this holds only during the time of treatment. Antibiotic-induced enhancement of the carrier state has also been demonstrated in mice (Bonhoff et al., 1962), and there is every reason to suppose the same would be true for food animals. Results of several tests, however, have been less than clear-cut. For example, Hobbs (1960) found an increase in carriers among experimentally infected chickens fed antibiotics over those untreated, and, similarly, Garside et al. (1960) found a striking increase in the frequency of carriage of Tc-_resistant_ _S_. _typhimurium_ as a consequence of tetracycline treatment. There was little or no effect, however, if the organisms remained sensitive. In this study, _Salmonellae_ could be recovered from about 10% of the chickens infected with sensitive organisms 70 days after infection, whether or not they were treated, and from well over 50% of those infected with resistant organisms and treated with chlortetracycline.

On the other hand, Jarolmen et al. (1976) failed to demonstrate prolonged carriage of Tc-sensitive salmonella after feeding to chicks either in the absence or in the presence of chlortetracycline in the feed. In this experiment, it is not clear that the salmonella strains used were _capable_ of establishing the carrier state since of some 200 infected chicks _no_ long term carriers were detected, whether or not the birds were fed tetracycline; moreover, _none_ of the infected chicks became ill, again regardless of whether or not they were

(in contrast, see below, Table 4, p.56).
given tetracycline/ Similarly, Evangelisti et al. (1975), in a *Salmonella* feeding experiment, failed to demonstrate any increase in *Salmonella* shedding in calves, pigs or chickens as a consequence of continuous tetracycline feeding. However, these latter experiments were continued for only 28 days which is not long enough to evaluate the occurrence either of chronic carriage or of resistance transfer from the resident coliform flora to the infecting *Salmonellae*. Post-treatment observation also was of insufficient duration to be meaningful. Moreover, the same *S. typhimurium* strain was used here as in the study by Jarolmen et al. (1976), and the question of its ability to establish the carrier state remains unanswered. In addition, these studies are both flawed by failure to perform the enrichment procedure that is necessary to detect low-level chronic *Salmonella* excretion (ASM-1974-Manual of Clin. Microbiol., Wash.,D.C., p. 194); further, there may have been active antibiotic present in the fecal samples, since these were obtained while the animals were receiving drugs or shortly after. In any case, there is always the problem of relating laboratory studies to the field situation where, as noted above, it has been found repeatedly that chickens (Lee, 1974; Pennington et al., 1968), pigs (Kobland et al., 1976), and cattle (Hinton and Williams, 1977) are frequent asymptomatic chronic *Salmonella* carriers, that these animals, especially pigs, flare en route to the abattoir, as they travel in crowded and unsanitary conditions and are stressed by such crowding and also by food and water deprivation (Williams and Newell, 1970). As a consequence, they excrete large numbers of *Salmonella* organisms that contaminate the carcasses and meat products; the *Salmonella* organisms isolated from animals and their products now show a high frequency of multiple resistance (Hinton and Williams, 1977; Neu et al., 1975; Wilcock et al., 1976; Procurull et al., 1971). The conclusion here seems

inescapable that studies such as those of Jarolmen et al. (1976) and Evangelisti et al. (1975) do not seem to reproduce adequately the conditions prevalent in the field, feedlot and abattoir and in addition, contain serious flaws in design. The type of study that would seem needed to evaluate the effect of antibiotic feeding on carriers is a field study in which a herd or flock with widespread endemic asymptomatic salmonellosis is split in two and fed antibiotic-supplemented vs. non-supplemented feed, with fecal samples cultured at appropriate intervals, and various tissues cultured at slaughter. So far as I am aware, such studies have not been done. The above-mentioned field study by Kobland et al. (1976) could possibly provide at least circumstantial evidence along these lines; a rather striking difference was encountered in the frequency of antibiotic resistance of *Salmonellae* isolated from hogs in different geographical locations; however, the antibiotic feeding history of these animals was not included in the report.

On the basis of these various results it can be inferred that animals fed antibiotics are more likely to become chronic carriers of resistant *Salmonellae* following infection than those not fed antibiotics, and it should be noted that if the results of Newell and Williams (1970) are valid, the results of field testing of animals are certain to underestimate grossly the true frequency of *Salmonella* carriage.

It may well be that the spread of *sensitive* *Salmonellae* can be controlled in the field by subtherapeutic levels of antibiotics and perhaps that treatment of active cases may also be effected. If these levels actually do inhibit sensitive *Salmonellae*, then it would seem probable that ultimately subtherapeutic antibiotics must promote the establishment of chronic carriage of *resistant* *Salmonellae*, since these have been shown repeatedly to emerge during subtherapeutic antibiotic feeding (Smith and Tucker, 1975a,b; Jarolmen et al., 1976).

An important question in this connection is whether animals (or for that matter, humans) are more susceptible to *Salmonella* infection if they are taking antibiotics than if they are not. Results of experiments with mice are strongly affirmative of an increased susceptibility (Bonhoff and Miller, 1962; Bonhoff, Miller and Martin, 1964; Meynell, 1963), and available evidence suggests that the same is true in humans (Adler et al., 1970).

The major route of transmission of *Salmonellae* from animals to man is via the food chain (see Fig. 2); meat, eggs and meat products are often heavily contaminated by *Salmonellae* from the animals themselves (Lee, 1974; CDC *Salmonella* Survey, 1976) and so initiate outbreaks of food-borne salmonellosis (CDC, 1974; Cohen and Blake, 1977). Secondary routes of transmission involve acquisition of the organism by farm workers directly from infected animals and more commonly, by meat production workers by contact with infected feces, carcasses, hair, etc. These individuals may then transmit the organism by any of a number of routes to other humans and may also spread it more widely to meat and other food products. *Salmonellae* are, of course, destroyed by cooking and so well-cooked foods are rarely a source of salmonellosis (unless they have been reinfected after cooking). However, consumers spread the organisms to other foods, some of which are eaten uncooked, and the organism themselves enhance the problem by multiplying at various stages along the food chain; this is one of the reasons why salads - with nutrient, neutral pH dressings such as mayonnaise - are a very common source of food-borne salmonellosis (Wiener, 1974; CDC 1973). In addition to infecting other foods, a housewife-consumer may transmit the organism from contaminated meat directly to her baby. The single infective dose for adults is evidently substantially larger than that for babies, especially those under one year of age. Babies are also a high risk group because of their tendency to do a lot of licking and sucking of various objects. These of course, are the underlying reasons why the vast majority of *Salmonella* infections occur in the very young.

It is significant also that although humans as well as animals may become carriers after *Salmonella* infection, the frequency and duration of the carrier state is very low in young adults, i.e., in those who are most frequently in contact with babies. Therefore, although it may be true that mothers and other attendants are the principle *vector* of salmonellosis in babies, they are rarely the *source* of the organism; that is, transmission to babies is much more often the consequence of handling contaminated meat, eggs and meat products than of chronic *Salmonella* carriage by these people.

Documentation for the entire animal→meat→mother→baby route of infection is often difficult to obtain. However, various parts of this route can easily be documented. In a *Salmonella* outbreak in Connecticut in 1976, for example, where the line of transmission was unequivocally demonstrated to be from infected calves to humans, three infants were secondarily infected by adults - one by its mother who was ill, two more by a nurse who was not (Cohen et al., 1977). In this case all isolates of the organism, *S. heidelberg*, were resistant to Cm, Su, Tc, and several were resistant to Nm, Sm and Nf as well. All of these resistances were transferable, in two blocks - Cm, Su, Tc, and Nm, Sm, Nf. *E. coli* with this same resistance pattern were isolated from two infected calves and from one human case; this particular resistance pattern was not seen in any of over 10,000 pathogenic *E. coli* strains isolated from the Northeastern U.S. in 1976, including 42 isolated from controls in the Connecticut study (Cohen et al., 1977).

The most dramatic, indeed frightening, example of *Salmonella* transmission direct from animals to man is the celebrated *S. typhimurium* type 29 epidemic that took place in England in the 1960's. Here, the multiresistant organism was transferred from infected calves (in which it caused devastating economic losses due to therapeutic failure) to man, where it caused several hundred cases and five deaths before finally being brought under control. This epizootic-epidemic was studied extensively by Anderson and coworkers (Anderson, 1968b)and will not be described in more detail here except to say that the spread of multiply resistant organisms among animals and from animals to man was promoted by prophylactic (i.e., subtherapeutic) levels of ampicillin as well as by therapeutic levels - both of which were, of course, futile.

As further evidence for the primacy of the food chain route, the frequency of egg-related outbreaks of salmonellosis has declined dramatically in recent years as a direct consequence of public health and sanitation measures put into effect to prevent the sale of contaminated eggs and egg products (Cohen and Blake, 1977). No such measures have been adopted for poultry and meat, and the frequency of meat and poultry-related outbreaks has, if anything,increased in the same period of time (Cohen and Blake, 1977). Therefore, *the contamination of foods is nearly always directly from animals*. If human carriers were involved to any appreciable extent, this pattern would not have been seen.

Other routes of transmission of salmonellosis include water supplies; here, it is often difficult to trace the transmission route, since animal wastes, human wastes and ground waters contaminated by wild animals such as birds, turtles and frogs may all contribute. In one well documented case (Harbourne, 1977) a human carrier of *Salmonella paratyphi B* infected a farm water supply. The cattle became infected by this route and then transmitted the organism to farm workers and other local people. This illustrates the complexity of recycling and transmission chains and also an additional feature of *Salmonella* epidemiology, namely recycling from man back to animals. By feeding infected feedstuffs to animals, man acts as a vector of salmonellosis in the farm animal infection cycle. This cycle helps to maintain the high level of salmonellosis endemic in farm animals and is responsible for the pandemic of S. agona traced to contaminated fish meal (Peruvian anchovies) used in animal feeds throughout the world (Lee, 1974).

Of course, Salmonella recycling among humans occurs also, both via carriers and by passive transfer between foods. As with animals, the carrier state is a more frequent sequel in those given antibiotics than in untreated cases, and antibiotic resistance develops in about 10% of initially sensitive strains as a consequence of treatment; so one component of any Salmonella control program is the treatment of uncomplicated enteritis by symptomatic measures only and the avoidance of antibiotics except where there are systemic complications (Aserkoff et al., 1970).

Again, regarding the source of Salmonellae on meat, it has been argued that this is a consequence of handling by human carriers (Walton and Lewis, 1971). Although this is surely possible and may account for a small part of the problem, in most cases where there is good documentation, it has been shown that the organisms on meat are the same ones that are isolated from the feces of the animals at the time of slaughter (Bettelheim et al., 1974). As one might expect, foodhandlers in institutions like hospitals, schools, restaurants, etc. are often responsible for spreading the organisms from contaminated meats to other foods; they may thus generate an outbreak in which they, themselves may also suffer. Incomplete epidemiology may then tend to implicate the foodhandler, who by this time has a positive stool, as the source of the outbreak when, in fact, he was merely a vector. The high frequency of egg contamination is a reflection of the high frequency of Salmonella carriage in chickens (Marx, 1969; Wiener, 1974). Since the contamination of eggs occurs, without the slightest doubt, during passage through the cloaca, the recent reduction in egg-related outbreaks resulting from the sanitization of eggs mentioned above again rules out any possibility that human carriers were ever the source.

As another unequivocal example of animal-to-man transfer of Salmonellae, albeit one that is not directly related to farm animals, I refer to the epidemic of S. litchfield and several host-adapted serotypes caused by pet turtles (Lamm et al., 1972). Here, some 300,000 cases of salmonellosis over a period of several years were all traced to infected pet turtles, although in some cases secondary spread among people clearly took place.

The passive transfer of Salmonella from contaminated meats to other foods is common and is a frequent cause of serious outbreaks, since the organisms tend to multiply better in certain other media than in meat itself (Wiener, 1974).

In conclusion, while it is not always possible to demonstrate epidemiologically the entire sequence of transfer from animal to food to human in any given case, the individual steps in the sequence have each been demonstrated repeatedly; taken together with the rarity of Salmonella carriage among young adults, these observations suggest strongly that the major reservoir of human salmonellosis in the U.S. is infected farm animals and that the major route of transmission is via the food chain. About 50% of all outbreaks of salmonellosis are caused by products of animal origin as the proximate source, and it seems likely that these sources are responsible for a similar proportion of the endemic cases. This is a conservative estimate of the true importance of Salmonellae of animal origin in human disease, since secondary spread to other humans also occurs following exposure to some human cases who acquired their organism from meat or animal products (CDC data; J.V. Bennett, pers. commun.).

(b) *E. coli*

The routes of exchange of *E. coli* among man, farm animals and other animals are clearly parallel to those for *Salmonella*, as shown in Fig. 2. Since *E. coli* is a normal inhabitant of the intestinal flora of both man and animals and since only a relatively small proportion of individuals contract *E. coli* disease, either spontaneously or as a consequence of contact, the epidemiology of *E. coli* transmission can most easily be traced *directly* by the use of genetically marked strains. It is abundantly clear from studies correlating biotypes isolated from various sources that there is a very considerable frequency of transfer of *E. coli*, including multiresistant strains, from animals to man by direct contact with animals, through contaminated environmental sources, and by contaminated meats and animal products. These are considered in turn as follows (indented sections in the following discussion are taken from the Federal Register for August 30, 1977, pages 43776-8):

> "(i) Direct contact with animals: A number of studies have shown that humans in contact with animals receiving medicated feed, including subtherapeutic levels of penicillin, have a higher incidence of drug-resistant organisms in their flora than do control populations without this direct contact. Linton et al. (1972) found a higher incidence of drug-resistant *E. coli* in adults employed with livestock husbandry than other rural or urban adults. Wells and James (1973) found a higher incidence of drug-resistant *E. coli* in humans in contact with pigs given certain antibiotics than in humans in contact with pigs that had not been given antibiotics.
>
> Siegel et al. (1975) compared the proportion of resistant organisms in fecal samples from: (a) people working on farms who were continuously in contact with the predominantly resistant flora of animals receiving subtherapeutic levels of penicillin; (b) people residing on the same farms with no direct exposure to the farm animals; (c) people treated with antibacterial drugs; (d) untreated people residing with treated

individuals; (c) untreated people with no exposure to farm animals or treated individuals.

The data (Siegel et al., 1975) indicate that the enteric flora of individuals not directly exposed to the selective effects of antibiotics can be affected by contact with animals; furthermore, these individuals may be affected by contact with other people who have a predominantly resistant flora as a result of their exposure to subtherapeutic levels of antibacterials in feeds.

A study sponsored by the Animal Health Institute, Levy et al. (1976b) examined the change in intestinal microflora of chickens, farm dwellers, and their neighbors before and after a tetracycline-supplemented feed was introduced on the farm. Within 1 week after introduction of this antibiotic in their diet, the *E. coli* of the chickens were almost entirely tetracycline resistant. Subsequently, at a slower rate, increased numbers of antibiotic-resistant bacteria appeared in the flora of the farm dwellers. No such increase was observed in the farm neighbors, who were not exposed to the animals fed subtherapeutic antibiotics. Within 5 to 6 months, 31.3 percent of weekly fecal samples from farm dwellers contained greater than 80 percent tetracycline-resistant bacteria compared to 6.8 percent of the samples from the neighbors. This is statistically significant ($P<0.001$). Using a specially marked resistance gene to identify a particular plasmid, Levy was also able to demonstrate the direct spread of resistant organisms from chickens to chickens and from chickens to man (Levy et al., 1976a)."

In another AHI-sponsored study, Hirsch and Wiger (1975) readily demonstrated transfer of R^+ *E. coli* from calves to their attendants (confirming the identity of the strains by genetic traits and by DNA base sequence homology study). In this study *in vivo* plasmid transfer in the calves was observed; however, the presence or absence of tetracycline in the feed had no apparent effect on plasmid transfer or upon transfer of the organisms to humans. Interpretation of these results in terms of the effect of antibiotics in feed is difficult or impossible because the fecal flora of the calves was highly Tc^r regardless of the presence of the antibiotic and because the "antibiotic-free" feed had 4 g/ton of Tc (there are no data on whether this level is sufficient to maintain a resistant flora or whether the resistant flora in this case persist in the absence of selection).

(ii) Contamination of the environment: Although the mammalian body is the primary reservoir of coliform organisms, these organisms are, inevitably, ubiquitous in the external environment where they often survive for periods measurable in months (Feary et al., 1972; Langlois et al., 1975). Presumably, the major route by which they reach the environment is via feces. Possibly the most modern sewage treatment facilities could eliminate the transmission through sewage of human coliforms to the environment. However, the total elimination of human fecal contamination of the environment is quite unthinkable, even in the most highly developed urban context, let alone in rural and "underdeveloped" regions. And as for animals, this possibility is hardly worth discussing. Coliforms are, in any case, ubiquitous in the soil, in sewage, in streams, lakes, rivers and coastal waters and wherever else there is direct or indirect fecal contamination (Langlois et al., 1975; Feary et al., 1972). Although in certain specific situations it is possible to say that the primary or even the only source of environmental coliform contamination is farm animals, it hardly matters in the overall picture; farm animals are without the slightest possible doubt the major source of environmental coliforms. And as 80% or more of farm animal coliforms carry plasmid-mediated antibiotic resistance, it is also an absolute certainty that resistant coliform organisms of animal origin contribute heavily to the environmental pool of such organisms. In fact, a very rough calculation will show that farm animals probably contribute somewhere between 99% and 99.9% of the resistant coliforms in the environment (see Linton, 1977).

This is because:

(a) About 10 chickens, about one-half of a turkey, about one-half of a pig and about two-tenths of a steer are slaughtered every year per person in the U.S. (1970 figures).

(b) Most of these animals are continuously fed antibiotics and so their coliform flora is predominantly resistant (50% to 80%).

(c) Most of the animal excreta reach the environment directly.

(d) The prevalence of resistance among human coliforms is much lower, especially for those not in contact with farm animals and not receiving antibiotic therapy (Linton, 1977).

(e) The bulk of human coliforms are destroyed by the processing of sewage.

"R-plasmid-containing bacteria occur in rivers and sea water, and some authors have urged stricter control of discharges to surface waters. Feary et al. (1972) examined the incidence of antibiotic-resistant E. coli present at sites along a fresh water river system and within the salt water bay into which it empties. Antibiotic-resistant coliforms were detected in nearly all the fresh water sites sampled and in about 50 percent of the salt water sites. Feary found that 20 percent of the 194 strains tested contained R-plasmids carrying multiple antibiotic resistance which could be transferred to sensitive Salmonella typhimurium, Shigella dysenteriae, and E. coli. They also isolated coliforms containing R-plasmids carrying resistance to chloramphenicol. Transferable chloramphenicol resistance is a significant health concern since chloramphenicol is often the antibiotic of choice for the treatment of typhoid fever. In Feary's study, the incidence of coliform organisms appeared higher around heavily populated areas, but coliforms were also recovered with ease from rural areas. In one case where particularly high counts were obtained, the sample was taken below a large cattle feedlot.

The high levels of resistant coliforms may be of more consequence in and from 4 of 50 specimens of cooked meat. Babcock et al (1973) isolated multiresistant *E. coli* from 80 percent of 98 samples of dressed beef. Resistance in most cases was found to be transmissible.

Similar incidents of *E. coli* contamination occur with the slaughter of chickens. Kim and Stephens (1972) found a high incidence of R-plasmid-bearing *E. coli* in "ready to cook" broiler chickens. The greatest number of *E. coli* isolated were obtained from the fluid and abdominal cavity, suggesting that the principal source of these microorganisms is the intestines. Furthermore, poultry meat has been incriminated as a source of *E. coli* for patients in hospitals (Cooke et al., 1971, and Shooter et al., 1970).

The presence of antibiotic-resistant (R-plasmid-bearing) *E. coli* in the animal intestinal tract and on the carcass does not conclusively prove that the *E. coli* are identical organisms. However, recent studies using serotyping methods have characterized resistant and sensitive *E. coli* isolated from the animal intestinal tract and carcass (Shooter et al., 1974; Howe, Linton and Osborne, 1976c; Linton et al., 1977a,b) and have found that the resistant O-serotypes on the carcasses of pigs, calves, and poultry frequently are identical to those isolated from the fecal contents of the same animal. Moreover, Linton et al. (1977b) showed that a large number of *E. coli* found on table-ready thawed chickens were resistant to therapeutically important antibiotics. The organisms reaching the kitchen included a wide diversity of O-serotypes of antibiotic-resistant *E. coli*. Similarly, Shooter et al. (1974) described the distribution and serotype of strains of *E. coli* from a poultry packing station and an abattoir. Shooter concluded that 'results in both the abattoir and the poultry packing station indicate that there is transfer of strains from the faeces of the animals to the environment and that the strains of *E. coli* found on the carcasses of poultry, cattle and beef will originate from the feces of the animal and from the environment and will reflect the history of the carcass.'"

Therefore, it is certain that there is free interchange of *E. coli* between animal species and human individuals. However, because of methodological difficulties, there are only a few well documented demonstrations of direct animal to man transfer of specific E. coli organisms. In one of these, Linton and coworkers (1977c) in a very careful study showed that multiresistant E. coli contaminating commercially purchased chicken meat transiently colonized an individual during the preparation of this meat for consumption.

The significance of this result lies primarily in the volume - some 2 x 10^9 chickens are eaten in the U.S. every year, and most, if not all, of these chickens are contaminated with E. coli, of which probably 80% are multiply resistant. Thus, even if only 1% of the chickens eaten result in colonization of the consumer by E. coli, this would represent many millions of colonizations every year. Moreover, plasmid transfer can take place even during a relatively short residence time for the donor strain (Smith, 1969).

With respect to E. coli infections and the sources of the causative strains, there are two situations to be considered: enteric and extra-intestinal E. coli disease. These will be considered separately, but it should be remembered that the primary source of the E. coli organisms that cause extra-intestinal infections as well as of those that cause diarrhea is the GI tract.

(c) Enteric-disease producing (EDP) E. coli

E. coli strains capable of causing diarrheal disease are referred to as enteropathogenic (if the mechanism is not fully known), as enterotoxigenic (if an exotoxin is involved), or enteroinvasive. In this section we shall be dealing only with the enterotoxigenic variety. In the case of E. coli causing diarrheal disease by the production of an exotoxin, brilliant studies by Smith and coworkers (Smith and Halls, 1968; Smith and Linggood, 1971, 1972) and by Falkow and coworkers (Gyles et al., 1974; So et al., 1975) have shown that the toxin (known as E. coli enterotoxin) involved is often encoded by plasmids that can be transferred from strain to strain, and that a second plasmid-coded gene product, the K-antigen, is also required for pathogenicity, enabling the organisms to adhere to the wall of the small intestine. Although the K-antigen does seem to show some species specificity, the enterotoxin does not. In any case, enterotoxic E. coli are highly infectious and cause rampant epidemics among calves, piglets and poultry, with substantial economic losses, as well as serious outbreaks in hospital nurseries. Although the transfer from animals to man of such strains or of enterotoxigenic plasmids has not been demonstrated directly, a number of food-borne outbreaks of E. coli diarrhea due to enterotoxigenic strains have occurred (Sack et al., 1977; Ørskov et al., 1977). In view of the usual animal source of food-borne coliforms, it is likely that animals were responsible here also. Moreover, it should be borne in mind that since the K antigen is often encoded by conjugative plasmids also, there are several potential genetic routes by which a strain enteropathogenic for animals may readily be converted into one capable of causing human disease.

The incidence of R plasmids is very high among enterotoxigenic E. coli strains from either animals or man (Smith, 1970; Gyles et al., 1974). The coexistence of Ent with R plasmids within the same cells raises the possibility of recombination, translocation, or independent cotransfer. If this occurred, selective pressure of antibiotics would facilitate the spread of enterotoxigenic determinants within the intestinal flora. An example of independent cotransfer of R and Ent has recently been analyzed in some detail by Wachsmuth et al., (1976). Here, a high-frequency of in vitro cotransfer was observed for an enterotoxin determining plasmid and an R plasmid from an E. coli strain responsible for a hospital outbreak of infantile diarrhea. This E. coli strain contained two plasmids. A 30 megadalton plasmid was associated with the production of heat stable enterotoxin, while a plasmid of 67 megadaltons determined drug resistance against seven antibiotics. When the R factor was transferred, 36% of the drug resistant recombinants also inherited the Ent plasmid (Wachsmuth et al., 1976).

Of even greater significance in the present context is the recent isolation from piglets with diarrhea of an *E. coli* strain carrying an Ent plasmid *with* resistance genes attached; this plasmid presumably arose naturally by recombination or translocation (Gyles, Palchaudhuri and Maas, 1977), and is conjugative, determines the production of both heat labile and heat stable enterotoxins and resistance to tetracycline, sulfonamide and streptomycin. To make matters worse, at least one conjugative plasmid encoding the K99 adhesion antigen (So et al., 1976) has also been found to carry resistance genes. If our experience with the buildup of multi-R plasmids is any guide, it should not be long before we see the grand plasmid marriage: a conjugative, Ent$^+$ K$^+$ R^{+++} plasmid all in one convenient, disease-causing package.

Thus, *antibiotic usage will select for enteropathogenicity simultaneously with resistance, and consequently, antibiotic usage will increase directly the frequency of E. coli disease in man*. As noted above, the first examples of animal-related *E. coli* diarrhea are just now beginning to occur - perhaps because it is only very recently that the enterotoxin-R gene, and K antigen - R gene linkages have been discovered. It is likely that these linkages have evolved only very recently, in response to the intensive antibiotic selection pressure that has led to the widespread increase of R$^+$ bacteria and to the development of plasmids with multiple resistance genes.

Other virulence factors in E. coli: hemolysins, hemagglutinins, and colicins and other toxins. Although *Escherichia coli* is usually part of the normal flora of man and animals, this organism is also the most common cause of urinary tract infection (UTI) and has been increasingly found in other extraintestinal EI) infections among hospitalized patients. In general, it is clear that the usual source of *E. coli* causing EI infections is the colon of the same individual.

Two views have been put forward to explain the source and nature of E. coli isolated from extraintestinal infection. One view holds that the E. coli causing infection are the most prevalent type in the feces and that these organisms are simply in "the right place at the right time". The alternative view is that organisms causing the infection have 'special' properties which permit them to initiate and sustain an extraintestinal infection. It now seems clear, that the latter hypothesis is correct. E. coli isolated from extraintestinal infection, whether from wounds, UTI, neonatal meningitis or the blood stream, in general are more likely than random fecal strains to: (1) be of specific serotypes - O6 and certain others being commonly associated with upper UTI infection (Ørskov et al.,1977), (2) be hemolytic, (3) produce colicin V, (4) carry the K1 antigen, (5) ferment dulcitol, (6) hemagglutinate human erythrocytes in the presence of 0.5% d-mannose, and (7) kill 13-day old chick embryos injected allantoically. The observed correlations are less than perfect. Not all E. coli strains isolated from extraintestinal infection possess each of these seven characteristics.

Colicins. Colicins are encoded by plasmids, many of which are conjugative, (called Col factors or Col plasmids). It had always been assumed that colicins were highly specific, affecting only bacteria related to E. coli, until recently when Smith and Huggins (1976) demonstrated that one of them, colicin V, was a virulence factor for various animals including chickens, calves and mice. Although the situation has not been fully analyzed, it is also clear that colicin V enhances both the ability to persist in the GI tract and virulence for humans and that hemolysins and hemaglutinins are also involved. Thus, Minshew and Falkow (1977) in a comparison of E. coli strains isolated from the human large intestine with those isolated from extraintestinal infections such as kidney infections and septicemia have found a number of highly significant biological differences. Seventy-five percent of *E. coli* from extraintestinal infections produce hemolysins, hemagglutinins, or both, whereas only 5-10% of colonic strains produce these substances; 12-18% of infecting strains isolated from blood or urine produce colicin V, whereas colicin V production in colonic strains is very rare (<1%). These differences are highly significant.

A striking finding with respect to *colonization* was reported by Smith and Huggins (1976), namely that oral administration of two ColV$^+$ bovine *E. coli* strains resulted in 100% replacement of the resident coliform flora in both of two different human subjects, without specific selection, whereas ColV$^-$ derivatives of these two strains were unable to colonize either of the same two individuals.

Yet another virulence-conferring plasmid has been identified by Smith (1974) in two *E. coli* strains causing bacteremia in lambs. This plasmid evidently encodes the production of a soluble toxin (distinct from enterotoxin) and is conjugative. Transfer of this *vir* plasmid was accompanied by transfer of antibiotic resistance; however, data on the question of physical linkage between the *vir* and resistance determinants are not presently available, nor is there data on the role of *vir* in human disease.

The existence of conjugative ColV plasmids carrying resistance genes has been known for some time (Delhalle and Gratia, 1976); hemolysin plasmids, though conjugative (Smith and Halls, 1967), have not so far been found to carry resistance genes (however, there has been very little work in this area).

With respect to ColV, at least, it is clear, therefore, that the *feeding of antibiotics can cause a direct increase in the pathogenicity of E. coli for man* as well as for animals, and can lead directly to an increase in the ability to colonize the human colon. There is, in addition, every reason to believe that the enhancement by colicin V of E. coli virulence and ability to colonize is not species-specific - a given colV plasmid will be as effective in man as in livestock.

In view of the recently described propensity of antibiotic resistance genes to translocate from place to place within the cell (Hedges and Jacob, 1974; Kleckner, 1977), it can be expected that resistance-carrying hemolysin plasmids, and any other plasmids imaginable, will soon be identified. Regarding plasmid carriage of the other virulence-related characters, O-serotype determinants are generally chromosomal, and there are no data on dulcitol fermentation or hemaglutinating activity. As mentioned above, certain K antigen determinants are clearly plasmid linked.

In addition to clearly definable determinants of pathogenicity, there are also correlations between serotype and frequency of isolation in association with certain pathological conditions. For example, the O6 serotype is very often associated with upper urinary tract infections and is, incidentally, one of the serotypes that is commonly resistant to multiple antibiotics. These correlations give rise to the concept of a continuum of pathogenic potential among E. coli strains. Insofar as selection for antibiotic resistance involves strains on the more pathogenic end of the continuum, antibiotic usage contributes directly to an increase in the reservoir of potential human pathogens - which will be multiply resistant into the bargain.

(d) Staphylococcus aureus

Thus far, there has been little consideration given to the possible problem of resistant staphylococci in connection with feed use of antibiotics. However, in view of the very high frequency of staphylococcal disease in farm animals as well as in humans, it would appear that an evaluation of the extent to which resistant animal staphylococci are selected by antibiotics in feed and transferred to humans via direct contact or via the food chain is very much in order as is a study of the relationship between R plasmids from human and animal strains. The primary reservoir of S. aureus is the mammalian skin and nasopharynx where asymptomatic carriage is the rule. This is common in pigs and poultry but rare in cattle. The factors that result in clinical infection are poorly understood, but presumably involve both host factors such as lowered resistance or immunity and bacterial factors such as increased virulence; although epidemics due to specific strains of S. aureus have been a very common experience in hospitals, the precise factors that result in the ability of a particular strain to do this in comparison to other strains to which we are continually exposed and which do not often cause significant infection are largely unknown. It is quite clear, however, that multiple antibiotic resistance is mediated by R plasmids that are transferable *in vivo* between strains (Novick and Morse, 1967; Richmond and Lacey, 1973) - albeit by a mechanism different from that in gram-negatives - and that such plasmids do not visibly compromise the virulence, infectivity, or survival of the organism. In fact, it has often been suggested that multiply resistant strains are, if anything, more virulent than sensitive strains.

There is ample documentation of transmission of staphylococci from asymptomatic human carriers to others who may become clinically infected. The occurrence of animal to man and man to animal transmission has also been clearly established, although in some cases, it is not always certain in which direction the initial transfer occurred.

Staphylococcal infections of abattoir workers and butchers are sufficiently common to have vernacular names. Pork workers refer to them as "pork infection", fish workers as "fish poisoning", inflamed puncture wounds are referred to as "starters", which, if not promptly treated with soaks and systemic antibiotics, develop into "septicemia" or "blood poisoning" (deep abscesses with fever, morbidity, lymphangitic spread and the possibility of serious sequellae) (see Ravenholt et al., 1961).

Smith and Crabb (1960) found that pigs and chickens are especially frequently colonized by coagulase positive staphylococci, that these become resistant as a consequence of antibiotic feeding, and that S. aureus were more prevalent on antibiotic-fed animals than on those not fed antibiotics (and,of course, the former were resistant). Moreover, staphylococci were readily exchanged between the animals and their attendants; in particular, when the animals were on antibiotics, the workers became colonized (nasal) or infected with resistant staphylococci.

Since animals fed antibiotics carry resistant staphylococci that are readily transferred to humans, when those who work with and process these animals become infected, they face therapeutic compromise due to the resistance of the organisms.

Additional evidence for farm-animal to man transmission of multiply resistant staphylococci has been presented by a number of investigators. Thus, Pagano et al., (1960) have described an epidemic of staphylococcal infection among veterinary students and presented evidence suggesting that various animals in the veterinary hospital were the source of the infecting strains. Similarly, Wallace et al. (1962) described staphylococcal infections among dairy workers in contact with cattle suffering from staphylococcal mastitis, again presenting evidence suggesting that the organism was transmitted from infected animals to humans; Roskey and Hamdy (1972) described an epidemic of staphylococcal infections among workers at a poultry processing plant, again with evidence that the birds were the source of the organisms. In many of these cases, the organisms were classed as the notorious 80/81 phage type that was responsible for extensive nosocomial and other epidemics in the 1950's and early 1960's. Among the animals and the humans involved in these studies were both asymptomatic carriers and clinically infected individuals, some with serious infections requiring antibiotic treatment. As the organisms were resistant to tetracycline, penicillin, streptomycin and, sometimes, erythromycin, a number of infected individuals had to be treated with chloramphenicol (Wallace et al., 1962) - a distinctly undesirable necessity. With respect to the question of "animal" vs. "human" strains, most writers accept the thesis that coagulase-positive staphylococci are species-specific; therefore, they generally list the "80/81" strains as "human" despite the findings that these strains may be carried chronically by animals, both with and without symptomatic infection. Thus, in a recent report of atypical staphylococcal mastitis in a dairy herd (Thawley et al., 1977) and in a report of staphylococcal infection and carriage by laboratory animals (Blackmore & Francis, 1970), the majority of isolates were referred to as more like typical "human" than "animal" strains. Nevertheless, the animals were chronically infected for many years or were chronic asymptomatic carriers. These types of observations tend to blur the epidemiological distinction between animal and human S. aureus nearly to the point of obliteration; whether or not humans may have been the original source of any of the animal infections is largely irrelevant. Humans and farm animals seem to trade strains rather freely; clinical infections of some severity are caused in both groups; and fully virulent, multiply antibiotic resistant strains are common in these situations and may seriously compromise therapy in animals as well as in man.

(e) Other species

Streptococcus agalactiae, a common cause of bovine mastitis, has been recognized more and more as a significant human pathogen, especially among the newborn. Although human and animal isolates are similar or identical and human isolates have been shown to be pathogenic for cows, direct chains of animal to man transmission have not been documented. Antibiotic resistance plasmids have been found in this species with increasing frequency; however, there are no data on the relationship of antibiotic feeding of animals to the emergence of resistance. Again, in the absence of data, the transmission chain must be regarded as probable but hypothetical.

Chlamydia psittacii. The primary reservoir of psittacosis is birds, and domestic poultry is an important component of that reservoir, especially with respect to those who handle poultry. Most human psittacosis is directly acquired from birds via the respiratory route. There is little secondary spread among people.

There are two ways in which antibiotic feeding to poultry results in a human health hazard. First, subtherapeutic tetracycline suppresses the symptoms of psittacosis (in turkeys) but does not eliminate the organism. Defeathering of the birds is probably the major mechanism of aerosol production, and workers are consequently infected by processing birds that appear clinically healthy. Second, in recent years, tetracycline resistant C. psittacii has been isolated and has infected humans in a turkey processing plant (Page, 1977). This is a clear case of therapeutic compromise, since tetracycline is the drug of choice for psittacosis.

It should be noted that psittacosis is not a benign disease; prior to the antibiotic era, the case fatality rate was as high as 18%. In more recent years, it has dropped sharply, presumably due to successful therapy. Thus, in one series of some 500 cases among turkey handlers, the fatality rate was about 2.4% (Graber and Pomeroy, 1958) - a figure which is still by no means trivial and which may start to rise again as Tc^r organisms become prevalent.

Mycoplasmas. Mycoplasmas are serious epidemic pathogens among farm animals, especially poultry. Some species have recently been found to carry plasmids; however, the question of antibiotic resistance is still an open one. Mycoplasmas also cause various diseases in man. However, the epidemiology of mycoplasmas is at present very sketchy, to say the least, and the question of resistance, its selection by antibiotics in feed, and transfer to man is entirely open and very much in need of data. Since erythromycin is the usual drug of choice for these organisms, there are grounds for concern over the increasing use of macrolide antibiotics as feed supplements.

Clostridia, esp. C. perfringens. *C. perfringens* is the cause of necrotic enteritis in poultry, infecting healthy birds by the oral route (Truscott and Al-Sheikhly, 1977; Berier et al., 1977) and is thought to be implicated in certain disease states in other animals. It is also a common cause of violent food poisoning, including a necrotizing enteritis that is commonly associated with pork and under those circumstances is known as "pig-bel", as well as gas gangrene in humans. Antibiotic resistant *C. perfringens* strains with transferable R plasmids have recently been isolated in France (Brefort et al., 1977) and in the U.S. Rood et al. (1977) have isolated multiply antibiotic resistant *C. perfringens* from the feces of pigs fed antibiotics. The development of multiple resistance in this case was postulated, therefore, to have been a consequence of antibiotic feeding. However, there has been as yet no example of human disease caused by such resistant *Clostridia*. It should be noted, however, that clostridial spores survive indefinitely in the soil and other environmental sites, and so will retain the potential to cause antibiotic-resistant human infections even if farm use of antibiotics is restricted. In this case, therefore, the damage is already to some extent irreversible.

For the sake of completeness, it should be pointed out that there are at least three situations where antibiotic therapy can be lifesaving in C. perfringens food poisoning. The first is the above-mentioned "pig-bel", where multiplication of the organisms is part of the pathogenetic process. The second is where an antispasomodic is mistakenly prescribed for control of gastrointestinal symptoms in the simpler type of enterotoxin poisoning. This retards the rate of clearance of the organisms permitting them to multiply in the bowel with potentially fatal consequences (H. Neu, personal communication). The third life-threatening C. perfringens infection is, of course, gas gangrene - fortunately an uncommon condition, but one that is a good candidate for therapeutic disaster if antibiotic-resistant spores from the feedlot find their way into a wound.

Yersinia enterocolitica and Y. pseudotuberculosis. These organisms, long known as epizootic species, are being recognized more and more frequently as a cause of often serious human disease. The primary reservoir for both is animals and there are well-documented cases of transmission from livestock, especially pigs, to man (see review by Bottone, 1977); moreover, conjugative plasmids carrying resistance to Cm, Sm, Su, Tc and Km and genetically related to known E. coli plasmids have recently been detected in human isolates of Y. enterocolitica (Cornelis et al., 1973; Bottone, 1977). Here, the epidemiological sequence of events has not been established; however, as with a number of species discussed elsewhere in this report, this is another example of a serious pathogen that has recently acquired R plasmids. Unlike some of the others, which are primarily human pathogens, these Yersinia species are primary animal pathogens, and it is, therefore, probable that farm animals are the major source of antibiotic-resistant strains as well as of sensitive ones.

Other zoonoses. Of the other zoonoses that are a human health problem, such as brucellosis, leptospirosis, listeriosis, erysipeloid, and glanders, antibiotic resistance has not so far presented a definable problem. Although Brucellae are gram-negative rods and are surely good candidates for plasmid transfer, I have found no data on this possibility. Still less is known of the possibility of plasmid-mediated resistance in leptospira. Listeria and Erysipelothrix are gram-positive rods and in view of recent evidence suggesting that gram-positive organisms may share pools of plasmids in much the same way that is characteristic of gram-negatives (see below), one should not treat lightly the possibility that either of these serious pathogens will acquire plasmids. In fact, as has been pointed out earlier in this report, there appears to be a "selective pressure threshhold" that once crossed results in the penetration by R plasmids of species barriers that were in all likelihood never previously breached. The fact that this has not yet happened to certain organisms despite twenty-five years of massive antibiotic dissemination is no reason to be confident that it will not; instead, it is a virtual certainty that it will happen, and probably fairly soon, if the massive overuse of antibiotics in animal husbandry and human medicine continues unabated.

3. Antibiotic resistant organisms and their conjugative R plasmids.

(i) Relationships between plasmids of various organisms.

Although the number of studies bearing on the relationship of plasmids from human and animal organisms is limited, all of the available data support strongly the thesis that R plasmids of enteric bacteria are drawn from a common pool.

Most studies have simply compared resistance patterns and have found nothing to distinguish animal from human strains in this respect. However, inasmuch as resistance patterns are not the most meaningful parameter in this regard, there seems to be little point in extensive documentation here. A more specific parameter is incompatibility specificity (Peyru et al., 1969). It is widely accepted among plasmid biologists that incompatibility type is a measure of relatedness among plasmids; incompatible plasmids are closely related, compatible ones are more distantly related, or unrelated. Extensive studies involving classification of plasmids by incompatibility have been performed both for plasmids of S. aureus (Peyru et al., 1969; Ruby and Novick, 1975), and for those of enteric organisms (Datta, 1975; Grindley et al., 1973; Chabbert et al., 1972) and have revealed some 10 different incompatibility types in the former and some 26 in the latter. In the enteric organisms, plasmids of certain incompatibility types show little or no preference for various bacterial species, whereas others tend to be associated more often with some than with others (Datta, 1975; Sato and Terakado, 1977). A detailed discussion of this situation is far beyond the scope of this report; suffice it to say that among the coli-salmonella-shigella group of organisms, there are no known barriers to the interspecific transmission of plasmids. Nevertheless, as isolated in the field, some E. coli serotypes carry R plasmids more commonly than others, and in one study (Petrocheilou and Richmond, 1976) three of the serotypes most commonly found to be carrying R plasmids, namely 08, 09, and 0101, were also three of the types most commonly isolated from both man and farm animals (Hartley et al., 1975). Similar results have been described by Linton (1977 - see Table 2). Those findings constitute strong evidence for the indiscriminate sharing of E. coli strains and their R plasmids between man and livestock.

In an extensive study of multi-resistant Salmonella strains from all over the world, Anderson and coworkers (1977) found that particular R plasmid incompatibility types were often localized geographically. The Andes, for example, seemed to act as a barrier that R plasmid-carrying Salmonellae did not seem to cross. In any event, in any given geographical location, the same R plasmids were found in all of the resistant Salmonella strains whether they were from animals or humans. In one particular case, a unique class H2 plasmid with an extremely unusual resistant pattern was isolated repeatedly from Salmonella strains both from animals and from humans, and it should also be pointed out that Salmonella typhi, an exclusively human pathogen, has been found to carry R plasmids, most notably ones carrying chloramphenicol resistance, that are very similar to plasmids carried by E. coli and by other strains of Salmonella. Here, one cannot easily document the route by which these plasmids made their way into S. typhi; however, the possible contribution of R plasmids coming from animals cannot be ignored.

The situation with respect to E. coli is similar (Datta, 1975). Added to these epidemiological studies demonstrating genetic relatedness are several studies at the molecular level leading to the same conclusion. Anderson and coworkers (1975) showed by DNA base sequence homology studies that plasmids of particular incompatibility groups were not always geographically localized but could in some cases be found worldwide and at times separated by at leas ten years. These results are summarized in Table 3, which is reproduced directly from Anderson et al. (1975). In all of 14 cases studied, plasmids of a given incompatibility group showed extremely high base sequence homology (the lowest degree homology in the study was 54%, and most were upwards of 85%). One particularly striking example was the finding of 100% homology between TP171 (isolated from a bovine S. typhimurium in England in 1972) and TP153 (isolated from a human S. typhi in Vietnam in 1974). These plasmids have molecular weights of some 57 million, which makes their identity all the more impressive. Similarly, TP120, from a human S. typhimurium in England was over 95% homologous with TP158, from a bovine strain isolated in Belgium. In general, little or no homology was the rule for plasmids of different incompatibility groups, regardless of their origins. In this study, incidentally, resistance pattern was not as well correlated with molecular relatedness as was incompatibility type.

In two carefully controlled recent experimental studies, direct transfer of R^+ bacteria from animals to humans was proven beyond any reasonable doubt. Levy et al. (1976b) used a test R plasmid with a highly distinctive thermosensitive chloramphenicol resistance marker as an epidemiological tracer. This plasmid in suitable E. coli hosts was fed to chickens and its direct transfer to two different humans in the study was readily demonstrated. Similarly, Linton et al. (1977c) demonstrated transfer of E. coli-containing R plasmids from contaminated chicken meat obtained commercially to a test subject who was given the chicken to prepare and eat by normal procedures. In this study, the identity of the chicken and human strains was established by antibiogram and serotype

TABLE 3*

Homology between plasmids of animal and human origin

The values indicate the degree of reassociation at 75 °C of ³H-labelled plasmid DNA with unlabelled plasmid DNA relative to the reassociation both with DNA of the same plasmid (= 100) and with *E. coli* K12 chromosomal DNA (= 0).

Unlabelled DNA from strains bearing plasmids			Labelled plasmid DNA											
			FII			I₁		N		H₁			H₂	
Group	Human (H) or animal (A) origin	Plasmid no.	240	R1-19K-	TP166	TP182	Δ	TP120	TP138	TP123	TP133	TP154	TP116	TP167
FII	H	240	100	57	54	14	13	0	0	3	—	4	0	3
	H	R1-19K-	—	100	93	—	—	—	—	17	—	—	—	—
	A	TP166	64	85	100	9	10	16	—	17	6	5	9	4
I₁	H	TP182	13	—	11	100	75	7	4	3	—	3	—	—
	A	Δ	13	—	11	65	100	1	0	—	—	4	0	0
N	H	TP120	1	—	4	0	1	100	94	5	—	0	0	1
	A	TP138	1	—	3	1	0	101	100	10	—	—	—	—
H₁	H	TP123	10	17	14	0	0	9	6	100	91	91	8	0
	H	TP133	—	6	12	—	—	—	3	94	100	75	3	0
	H	TP183	10	6	9	1	0	8	4	88	96	82	7	5
	A	TP171	—	—	—	—	—	—	—	—	100	—	—	—
	A	TP154	6	0	8	0	0	7	12	87	92	100	0	0
H₂	H	TP116	2	—	—	—	0	2	—	4	0	—	100	63
	A	TP167	—	—	—	—	—	—	—	—	0	—	81	100

The broken line encloses reactions of labelled plasmid DNA with unlabelled plasmids from the same compatibility group.
—, Not done.

*Anderson et al., J. Gen. Microbiol. 91:376-382,1975.(Table 3).

and the identity of the plasmids from the human and chicken strains was established by the powerful new technique of DNA fingerprinting by restriction endonuclease digestion. Identical fingerprints were found, indicative of identical plasmids. The probability of this happening by chance is essentially zero. A particularly significant finding in this study was that although only one of five test subjects was colonized by E. coli from the chicken meat, no less than five different resistant E. coli strains from the chicken meat ended up in the colon of this subject, all as a consequence of preparing the chicken for the table (but not as a consequence of eating it - which is expected since cooking should normally destroy the organism). Similarly, direct transfer of bovine R^+ E. coli to man has been observed by Hirsh and Wiger (1975), as mentioned previously.

This series of studies shows conclusively that R plasmids from animals and humans are indistinguishable, that direct transfer from animals to man is readily demonstrable when a suitable experimental model is employed, and that one may expect to encounter large individual differences among humans - and, for that matter, among animals - in the frequencies with which these events can be detected.

There are no data at present on the relationship between plasmids from animal and human staphylococci and streptococci. However, since multiply resistant staphylococci occur in both animals and humans, and since staphylococci are readily exchanged, there is little doubt that the R plasmids will turn out to be similar or identical. Sill less is known of the streptococci; however, as S. agalactiae is being more and more frequently recognized as a cause of human illness, and since it also carries R plasmids, it is probable that animal to human plasmid transmission will be found here also.

(ii) The effect of R plasmids on bacterial adaptivity.

It is presently the experience of most veterinary microbiologists that the intestinal coliform flora (and probably a good deal of the extraintestinal aerobic microflora as well) of farm animals includes a high proportion of multiply resistant organisms endowed with R plasmids *whether or not the animals have ever been fed antibiotics*. The same is clearly not true of humans (Hartley and Richmond, 1975), even those that work on farms or in hospitals (although I would like to see data on people such as those who have taken penicillin or tetracycline for many years and then stopped). There are probably two reasons for this difference, namely recycling of organisms and adaptivity, and it is difficult to say how much each contributes. The point, however, is that R plasmids, in and of themselves, must not detract seriously from the adaptivity of their host strains. Given a sufficient length of time in the presence of selective pressure, a high d-gree of fitness evolves for the host-plasmid complex so that the strain is fully adaptive in the absence of the selective pressure due to the antibiotic. In the farm situation, recycling of resistant organisms through the feed (Joynson and Howells, 1974; Margurd et al., 1975) and other routes certainly contributes substantially to the maintenance of a highly resistant flora, especially with regard to pigs.

Nevertheless, it is obvious that the presence of a plasmid must impose a finite metabolic burden on its host - to a first approximation, in proportion to its size. This has been repeatedly demonstrated in the laboratory where an R$^-$ strain eventually outgrows its isogenic R$^+$ derivative not only in the test tube but also within the experimental animal (Anderson, 1974). These apparently contradictory facts can be reconciled by the realization once again that despite the best of intentions, it is very difficult or impossible to reproduce satisfactorily field conditions in the laboratory.

Among the problems that one encounters are very simple ones: competition in nature is rarely between isogenic R^+/R^- organisms but rather between various unrelated organisms, some R^+ and some R^- (Hartley and Richmond, 1975); naturally-occurring bacteria of various species very commonly carry several different plasmids. These often lack identifiable functions, and so it is usually impossible to evaluate their adaptive value to the organism. However, naturally-occurring strains of a given species vary greatly in their plasmid content, and so it is clear that plasmids are in general neither essential nor do they impose a significant metabolic burden on their host organisms.

In fact, as mentioned earlier, the general inconstancy of intestinal flora is probably a much more important factor determining the persistence of an intestinal coliform strain than is the presence or absence of R plasmids in that strain. For example, Hartley and Richmond (1975) in an extensive monitoring survey, found that R^+ E. coli O serotypes had a longer mean residence time in the human colon, in the absence of antibiotics, (6.6 days), than R^- O serotypes (5.7 days). Note that even though these strains were not administered experimentally but were natural components of the colonic flora, their mean persistence times were quite short - certainly similar to what is obtained by feeding and usually referred to as "transient colonization". Moreover, inasmuch as in vivo resistance transfer in the absence as well as in the presence of antibiotics is commonplace (Smith, 1969; Smith and Tucker, 1975a; Jarolmen et al., 1976; Hirsh and Wiger, 1975; Petrocheilou et al., 1976, 1977), it seems likely that even these relatively short persistence times are ample for the occurrence of transfer. It must be emphasized in this connection that very few careful prolonged monitoring studies of intestinal flora have been done so that extensive data on in vivo persistence of R^+ strains and R transfer are relatively scarce. It is all the more significant, therefore, that most of these studies have shown that R^+ bacteria are not especially disadvantaged as a class and that R transfer takes place sufficiently often to be readily demonstrable in the absence as well as in the presence of antibiotics.

(iii) Effect of R plasmids on virulence.

If plasmids exact a metabolic price for their maintenance, perhaps they may thereby compromise the general disease-causing ability of their host strains. If this happened to a significant extent, then obviously R plasmids would be a public health blessing rather than the enormous hazard that they, in fact, represent. This hazard is exemplified by several recent major epidemics of salmonellosis and shigellosis involving many thousands of deaths and caused by multiply resistant, plasmid-carrying strains. In fact, I am not aware of a recent major epidemic of either of these diseases that was not caused by a multiply resistant strain.

In recent years, innumerable deaths due to therapeutic failure have been caused by multiresistant Proteus, Klebsiella-aerogenes, Pseudomonads, Serratia Streptococci, Staphylococci, Hemophilus, and Pneumococci, to name just a few, and now we have resistant gonorrhea to contend with. I have not heard claims that any of these organisms are enfeebled by the possession of plasmids; in fact, it was fairly well established in the early 1960's that multi-resistant S. aureus were more virulent than sensitive strains, which is not to say that the plasmids were necessarily responsible for the increased virulence, but simply that they were obviously no great handicap.

One could quote virtually the entire literature on the therapy of bacterial diseases during the past thirty years in support of the fact that multiresistant strains are fully virulent. Reports such as that of Jarolmen and Kemp (1969), describing preferential R factor reception by rough, avirulent Salmonella variants and claiming that R^+ strains are therefore less virulent may be interesting laboratory observations but are totally irrelevant to the question of R factors as a public health hazard.

One well-designed laboratory experiment seems worth quoting in this context, namely that of Smith (1972). In this study, a large number of R plasmids were transferred in vivo to a highly virulent strain of S. typhimurium and all were then subjected to a simple chick mortality test for virulence. By this simple test, the R^+ derivatives ranged from fully virulent to avirulent (2 cases). While there was in some cases a reduction in virulence, this was surely not the rule (see Table 4), and, in any case, these strains had not run the gauntlet of natural selection - which is required for all naturally-occurring resistant organisms.

(iv) New R plasmids in pathogenic organisms not commonly associated with animals.

During the 30-odd years since the introduction of antibiotics into medicine and animal husbandry, there has been a steady increase in the frequency of multiply resistant bacterial pathogens and commensals associated with humans and livestock. Until very recently, this phenomenon could be accounted for by antibiotic selection of preexisting plasmid-bearing organisms, by plasmid gene translocation, and by plasmid transfer to related strains. Over the years, these processes have led to the development of strains of certain species, notably Pseudomonas and Serratia, that are resistant to all usable antibiotics; with respect to treatment of infections caused by such organisms, we are now back in the pre-antibiotic era; and it is to be expected that unless the general usage of antibiotics is drastically curtailed, the number of fully resistant strains will continue to increase.

TABLE 4.§

Mortality rate amongst groups of 100 chicks infected with different R^- and R^+ strains of Salmonella typhimurium no. 98 (phage-type 14)

Strain number	Transmissible resistance pattern*	Percentage dead at the following days after infection													
		1	2	3	4	5	6	7	8	9	10	11	12	13	14
22	None	0	0	0	18	43	55	64	69	78	83	87	91	92	93
25	None	0	1	4	25	59	75	78	82	83	88	91	91	91	91
1	None	0	0	4	29	49	58	66	72	74	79	82	86	89	89
1	None	1	3	12	43	55	62	68	72	74	79	82	85	87	88
39	ASN	0	1	1	31	53	73	77	80	81	83	84	87	88	88
33	ASN	0	1	7	31	59	76	77	80	82	84	84	85	87	87
2	T	0	0	5	35	51	58	62	68	69	74	75	77	77	77
16	ASTN	0	1	2	19	35	44	52	57	62	70	73	75	77	77
44	ST	0	0	0	9	24	36	47	56	59	65	67	73	75	77
18	SSuTC	0	0	1	11	30	46	52	58	60	66	72	75	75	75
12	SSuC	0	2	13	29.	40	47	51	57	60	65	69	70	70	70
13	STN	2	2	3	8	25	31	32	36	42	44	49	51	52	52
3	ASSuCN	1	1	1	11	15	22	24	29	32	36	42	46	50	50
72	ASSuTCN	0	1	2	3	3	3	3	3	3	3	3	3	3	3
46	ASSuCN	0	0	0	0	0	0	0	0	0	0	0	1	1	1
nal^r 1†	None	0	1	3	11	23	27	30	34	37	46	49	51	51	51
nal^r 5	ASSuN	0	0	0	8	13	19	23	24	25	30	30	30	34	34
nal^r 7	AssuTN	0	0	0	3	4	7	9	11	14	20	22	24	25	26
nal^r 6	ASSuCN	0	0	1	4	6	7	10	12	16	17	19	19	24	24
nal^r 3	T	2	2	6	9	12	14	15	17	18	20	20	20	22	22
nal^r 8	SSuTC	2	3	6	9	11	11	13	14	14	15	16	19	19	19
nal^r 4	ASSuC	0	0	0	4	7	8	10	11	13	13	14	16	17	17
nal^r 2	ASN	2	2	2	3	3	6	6	6	6	9	9	10	10	10

* A = Ampicillin, S = streptomycin, Su = sulphonamide, T = tetracycline, C = chloramphenicol and N = neomycin.

† nal^r = Nalidixic acid-resistant mutant.

Each chick was given $7{\cdot}5 \times 10^9$ viable organisms of *S. typhimurium* strain 98 during its 1st day of life.

§H.W. Smith (1972). J. Med. Microbiol. 5:451-458 (Table II).

In addition to this more or less predictable process, recent years have witnessed a new and still more alarming development, namely the penetration by resistance plasmids for the first time of several hitherto impenetrable taxonomic barriers. The consequences of this have been grave and sometimes lethal.

In particular, clinically important human pathogens including *Hemophilus influenzae*, *Neisseria gonorrhea*, and, very recently, *Streptococcus pneumoniae* have all become resistant to one or more of the antibiotics that have hitherto been uniformly successful in the treatment of infections caused by them. In the case of the two former organisms, plasmids related to those found in gram-negative enteric organisms are responsible. In the latter, information on the genetic basis of the multiple resistance is not yet available. In addition, the primary animal pathogen, *Y. enterocolitica*, has also recently acquired R plasmids (Cornelis et al., 1973), and it is to be expected that other pathogenic microorganisms will soon do likewise. In none of these cases is the source of these plasmids clear; there is no evidence on whether the plasmids in question were derived from animal or human sources. The principle that is evidently at work here, however, is a very basic one - namely that the intense worldwide selective pressure exerted by antibiotics has given rise to an environmental load of R plasmids that is so great that extremely rare events - events that might never have taken place otherwise - are occurring; the cup runneth over, as it were. Although some of the plasmid transfers in question may have taken place in a human setting, the fact simply cannot be ignored that as farm animals are responsible for at least 99% of the R plasmid-carrying enteric organisms now present in the environment in this country, it is unthinkable that antibiotic usage in animals has not played at least an indirect role in these developments.

Conclusions

(i) Multiply antibiotic resistant coliforms, enteric pathogens, staphylococci and other organisms are widely prevalent in the environment and in the florae of farm animals and man as a consequence of massive antibiotic usage in animal husbandry and human medicine.

(ii) Although there may be minor differences between "animal" and "human" strains for some species, these present little if any barrier to the free transfer of multiply resistant bacterial organisms from animals to man via direct contact, via the environment, and via the food chain.

(iii) These multiply resistant organisms interact with man either by direct colonization, by clinical infection, or by transferring R-plasmids to the human flora and so constitute a substantial hazard to human health due to therapeutic compromise.

(iv) In several cases, resistance genes have been found genetically linked to plasmids that are themselves directly responsible for pathogenicity or for ability to colonize. Here, antibiotic feeding is directly responsible for an increase in human disease.

the salt water since certain sections are utilized heavily by fishermen in harvesting fish, shrimp, clams, and oysters. Oysters and clams are of primary concern because they continuously filter water and concentrate bacteria in their gut and they are often eaten uncooked.

Recent reports by Cooke (1976) have also described a high incidence of resistant coliforms in marine shellfish and freshwater mussels.

Therefore, the environment is heavily contaminated with bacteria containing transferable R-plasmids. Man is exposed to the danger of acquiring R-plasmid-bearing coliforms from the environment, and the relative number of R-plasmid-bearing bacteria is increased both by the subtherapeutic use of antibiotics in animal husbandry and the use of antibiotics in human medicine. Antibiotic-resistant bacteria are now so widely distributed in the general environment that it is difficult to relate their appearance to a particular use."

(iii) Contamination of food: "To assess adequately the significance of the problem of human food contaminated with E. coli, Howe and Linton (1976) described four factors that must be measured: (a) The incidence of R-plasmid-bearing E. coli in food-producing animals; (b) the load and frequency of excretion of E. coli from these animals; (c) the degree and source of contamination of carcasses at slaughter; and (d) the overlap of E. coli serotypes in various host animals with those commonly found in humans."

The role of antibiotic feeding in the development of a multiresistant coliform flora in livestock is documented elsewhere in the FDA report.

"These animals clearly constitute a reservoir "rich" in R-plasmids. Moreover, they excrete a large variety of distinct serotypes of E. coli.

During the slaughtering process, contamination of carcasses with intestinal microorganisms cannot be prevented. Meat and meat products are often contaminated with antibiotic-resistant E. coli, and these often reach the human consumer. Walton (1970) demonstrated that 52 percent of the bovine (beef) and 83 percent of porcine (pork) carcasses slaughtered at commercial abattoirs were contaminated with E. coli. Walton and Lewis (1971) isolated resistant E. coli from 21 of 50 specimens of fresh meat

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Dissemination of an Antibiotic Resistance Plasmid in Hospital Patient Flora

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The 2″ aminoglycoside nucleotidyltransferase, AAD (2″), which adenylates gentamicin, tobramycin, and kanamycin, became prevalent over several months in multiple strains and species of *Enterobacteriaceae* isolated at one hospital. Eight plasmids with the gene for this enzyme purified from different strains and species isolated at different times had similar *Eco*RI digestion fragments, indicating that the gene had disseminated on one plasmid without transposition. This 56.5-megadalton plasmid of incompatibility group M, which also carried three other resistance genes, spread, at first, largely in one strain of *Klebsiella pneumoniae*, which later disappeared. It transferred to some strains which tended not to colonize other patients and later circulated predominantly in *Serratia marcescens*. Computer surveillance of routine hospital laboratory results was able to detect and trace the gene and the plasmid and measure their effect on resistance prevalence.

An antibiotic resistance gene may transpose from one plasmid to another, may transfer on a plasmid from one bacterial cell to another, or may remain in a bacterial cell which leaves one person and colonizes another (8). In clinical settings, however, it has proven difficult to observe movement of resistance genes relative to plasmids, bacteria, and people because it has been difficult to identify individual genes, plasmids, and strains of bacteria at the same time. We describe here an occasion on which such observations were possible. They show the dissemination of a single plasmid into multiple strains and species of *Enterobacteriaceae* isolated from many patients in one hospital.

MATERIALS AND METHODS

The 330-bed general hospital was included in the International Survey of Antibiotic Resistance Prevalence, and the methods for susceptibility testing, computer filing, and analysis of results have been described previously (14, 16). Biotyping was performed by the API method (Analytab Products, Inc., Plainview, N.Y.). Serotyping was performed by the Center for Disease Control (Atlanta, Ga.). Plasmid molecular weight was determined by Alan Jacob. Aminoglycoside enzymes were identified by the method of Benveniste and Davies (1), and several of the earlier assays were performed by David I. Smith or Peter Kresel. β-lactamases were identified by isoelectric focusing in polyacrylamide gel developed with chromagenic cephalosporin (13). Methods for determining plasmid incompatibility have been described (3).

Plasmids were transferred to the *Escherichia coli* K-12 strain DR 25, an azide-resistant mutant of W3101. Plasmid DNA was isolated by the cleared-lysate method of Hansen and Olsen (10), modified for larger volumes, and further purified by CsCl-ethidium bromide centrifugation (20). Purified plasmid DNA was digested with *Eco*RI (New England Biolabs, Beverly, Mass.) in a reaction mixture containing 7 μg of deoxyribonucleic acid (DNA), 0.1 M tris-(hydroxymethyl)aminomethane (Tris)-hydrochloride (pH 7.5), 0.06 M NaCl, 0.01 M $MgSO_4$, and 5 units of *Eco*RI in a total volume of 100 μl at 37°C for 1 h with enzyme re-added at 30 min. Digests were electrophoresed on agarose gel (21) and visualized by ethidium bromide staining. The ability of the gentamicin or ampicillin resistance genes of transconjugant 1 (Table 1) to transpose to the genome of phage λ or the *Salmonella* phage P22 was tested as described by Kleckner et al. (11), with the plasmid also transferred to DB 6868, a plasmid-free derivative of *Salmonella typhimurium* LT2.

RESULTS

Figure 1 shows the results of routine susceptibility testing to six antibacterial agents of all clinical isolates of *Klebsiella pneumoniae* and *Serratia marcescens* at the hospital in 1975 and 1976. Although gentamicin had been used in the hospital since 1970, strains of these or other *Enterobacteriaceae* resistant to gentamicin were rarely isolated through 1975. Very few of the 1975 isolates in Fig. 1 have zones of inhibition around the gentamicin or tobramycin disks of less than 15-mm diameter. In 1976, however, there was an appreciable population of *K. pneu-*

TABLE 1. *Isolates selected for plasmid analysis*

Mo of isolation	Source	Species	API biotype	*E. coli* K-12 transconjugant no.
2/76	Blood	*K. pneumoniae*	5205773	1
6/76	Blood	*S. marcescens*	5317720	2
8/76	Blood	*Enterobacter aerogenes*	5305773	3
9/77	Blood	*S. marcescens*	5317761	4
10/77	Blood	*K. pneumoniae*	5215773	5
3/76	Wound	*E. coli*	5144552	6
4/77	Wound	*Morganella morganii*	0174000	7
4/76	Urine	*C. freundii*	1404572	8

moniae isolates with a peak of distribution at 15 mm, which constitutes a shoulder to the left of the susceptibility peak. Minimal inhibitory concentrations of gentamicin for representative isolates of this subpopulation were in the range of 8 to 32 μg/ml. Similar but more distinctly separated populations of *K. pneumoniae* that were moderately resistant to tobramycin and kanamycin appeared in 1976, as did *S. marcescens* populations resistant to gentamicin, kanamycin, and tobramycin. In 1976 there were also appreciable increases in the percentages of these isolates resistant to chloramphenicol and sulfonamides and in the percentage of *S. marcescens* isolates resistant to carbenicillin.

The isolates of *K. pneumoniae* with reduced zones of inhibition to gentamicin are shown in Fig. 2 to be the same ones which had reduced zones to tobramycin. Also, whereas fewer than a third of the other biotypes of *K. pneumoniae* had the reduced zones, virtually all that belonged to the biotype API 5205773, a biotype distinguished principally by a negative urease reaction, had them. Eight randomly chosen isolates of this biotype serotyped as type 2, whereas seven isolates chosen randomly from among five other biotypes were of five other serotypes.

The sequence of appearance of gentamicin-resistant *Enterobacteriaceae* is shown in Fig. 3. From February through May of 1976, 43 patients had gentamicin-resistant isolates of the single biotype of *K. pneumoniae* API 5205773. Thereafter, the rate of isolation of this biotype declined abruptly, and it was isolated from only two patients in all of 1977. During the four-month period, however, the rate of isolation of other gentamicin-resistant *Enterobacteriaceae* had increased sevenfold, and it remained elevated throughout 1977 although it has subsequently declined.

In all of 1976 and 1977, 372 patients had a total of 2,020 isolates of 49 different biotypes of gentamicin-resistant *Enterobacteriaceae*, 42% of them from urine, 23% from sputum, and 3% from blood. The patients were from all of the hospital's pavilions with 31% of them from the intensive care unit. Length of hospitalization at first isolation per patient, which averaged 6 days for other *Enterobacteriaceae*, averaged 24 for the resistant isolates, suggesting that their circulation was nosocomial (15). Of the 188 isolates of gentamicin-resistant *E. coli*, 149 came from patients who also had a gentamicin-resistant isolate of another species.

A total of 23 isolates of *Enterobacteriaceae* with the characteristically reduced zone diameters to gentamicin and tobramycin were tested for aminoglycoside-inactivating enzymes, and all were found to have the 2″ aminoglycoside nucleotidyltransferase, AAD (2″), which adenylates gentamicin, tobramycin, and kanamycin (6). *Enterobacteriaceae* resistant to gentamicin were usually also resistant to chloramphenicol (92%), sulfonamides (98%), and ampicillin and carbenicillin (94%), and resistance to all of these agents proved transferable to *E. coli* K-12 in mating experiments. The eight transconjugants listed in Table 1 had all acquired the TEM 1 β-lactamase. Plasmids of 19 of the isolates were grouped and belonged to incompatibility group M. Plasmid mass was 56.5 megadaltons. Isolates of biotype API 5205773 also had transferable resistance to tetracycline (77%) and to very high concentrations of streptomycin (83%) and kanamycin (83%), which was rare in other biotypes of *K. pneumoniae* and thus further confirmed the specificity of this biotype. Resistance to all of these agents segregated when isolates of API 5205773 were passaged in vitro, but the biotype remained unchanged.

Plasmids from eight of these gentamicin-resistant isolates which differed in species or biotype and month of isolation (Table 1) were each transferred in vitro to an *E. coli* K-12 and then extracted and digested with the *Eco*RI restriction endonuclease. The resulting DNA fragments were separated by agarose gel electrophoresis, as shown in Fig. 4. The fragments of each of the plasmids of transconjugants 2 through 7 of each appear to form 13 bands which have

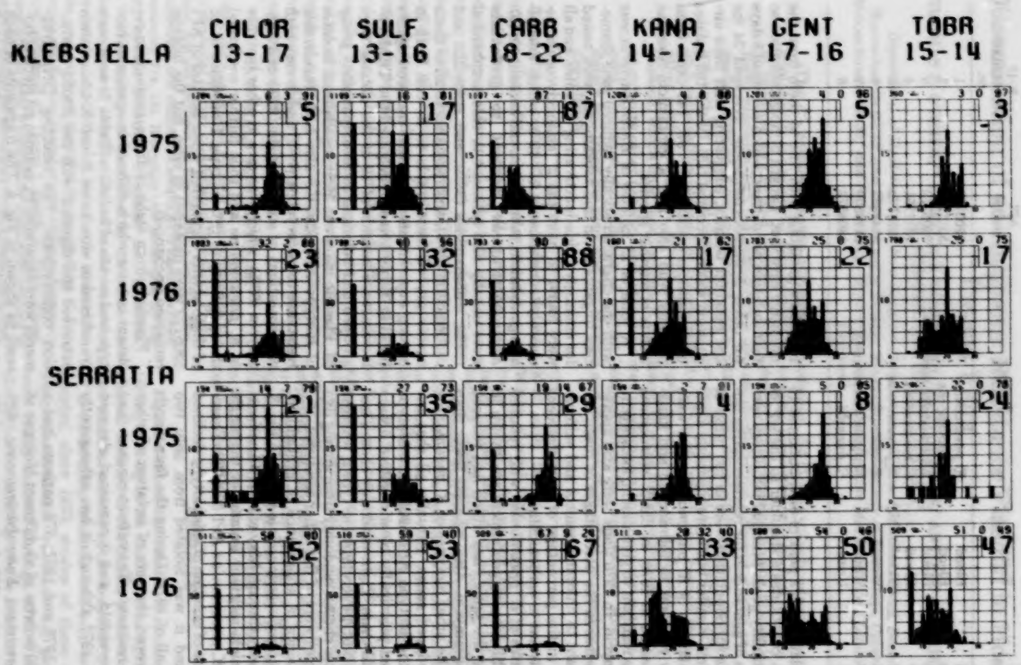

FIG. 1. *Computer-generated histograms of frequency distribution of diameters of zones of inhibition around susceptibility test disks. Vertical lines are at 5-mm intervals, and the horizontal scale (percent) shifts to accommodate data. Breakpoint limits of intermediate zone, here adjusted for thinner plates, are printed under antibacterial label. The large number in the upper right corner of each histogram is percent unrepeated isolates that are resistant.*

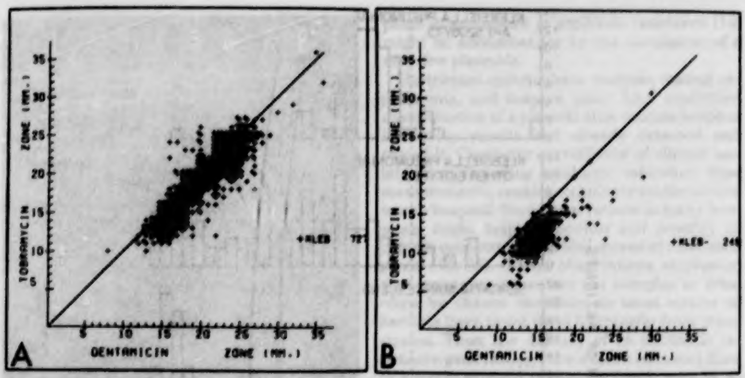

FIG. 2. Computer-generated scatter plot of diameters of zones of inhibition around gentamicin and tobramycin disks for consecutive isolates (in 1976) of K. pneumoniae biotypes other than API 5205773 (A) and of only that biotype (B).

corresponding positions in the gel. Transconjugant 1, which has a plasmid from one of the early isolates of API 5205773, has the same bands but has an additional large fragment band as well. Transconjugant 8, which has the plasmid from a *Citrobacter freundii* isolate carrying a tetracycline resistance gene not carried by the other isolates, has a similar additional large fragment band and is missing at least three of the smaller fragment bands which the others have.

DISCUSSION

The abrupt emergence of gentamicin resistance observed here suggested spread of a single aminoglycoside resistance gene. This was further supported by the similar pattern of reduction of zones of inhibition around gentamicin, tobramycin, and kanamycin disks observed with all of the resistant isolates, and by the finding of the same aminoglycoside-inactivating enzyme in all that were tested. Incompatibility grouping suggested, and restriction endonuclease digestion analysis confirmed (7, 18), that the plasmids carrying the gene in different species were identical or nearly so and, by inference, that the genes were also.

Routine biotyping of all clinical isolates of *Enterobacteriaceae* showed that the plasmid spread at first mostly in one strain of *Klebsiella* with the biotype API 5205773. Later, this strain practically disappeared from the hospital, but by then the plasmid was in many other strains. The number of strains may be overestimated by the number of biotypes since the stability and reproducibility of each biotype has not been established as it has for API 5205773. Enough markers differ, however, to suggest multiple strains within most species, and at least six species were involved. In other hospitals gentamicin resistance has been observed to appear in multiple species as here (2, 5, 7, 9, 22, 23), or mostly in one species (17) or one strain (4, 19), suggesting that the extent of plasmid transfer may vary from outbreak to outbreak.

A previously rare resistance gene could become prevalent in multiple strains of *Enterobacteriaceae* in a hospital if each strain were introduced separately with individual patients admitted from a community where such strains had suddenly become widespread. Alternatively, the gene could have entered in one or a few strains and subsequently transferred to other strains circulating in hospital patient flora. Such transfer in hospital seems far more likely here. The gene was predominantly associated with species of bacteria that are commonly nosocomial and infrequently isolated from community flora. Four other hospitals in the area monitored by the same computer program had no concurrent increase in gentamicin-resistant isolates of *Enterobacteriaceae*. Patients had been hospitalized four times longer before having an isolate of *Enterobacteriaceae* with the gene than one without it. Moreover, while *E. coli* is the most commonly isolated of the *Enterobacteriaceae*, four-fifths of the isolates of *E. coli* with the gene were from patients who also had isolates of other species with the gene.

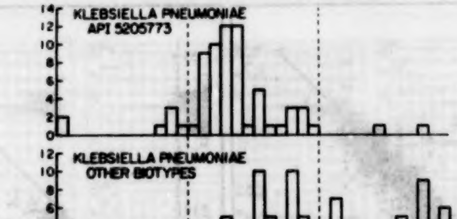

FIG. 3. *Number of patients in the hospital each month who had their first isolate of a species of gentamicin-resistant Enterobacteriaceae.*

Some strains which had the plasmid, e.g., those of *E. coli*, were usually isolated only from patients who also had other isolates with the plasmid. Epidemiologically, these strains may have been "blind-end" plasmid recipients, poor at colonizing other patients. The plasmid ultimately came to spread mostly in *S. marcescens*, which appeared to displace the *K. pneumoniae* API 5205773 in which it spread earlier. Plasmid transfer may thus eventually have produced an association of a needed resistance gene with the chromosomal traits best suited for survival and spread in the hospital. If so, there would be no further selection for transfer function, which appears to have been lost in the later phases of some other outbreaks (12, 17).

The absence from the digests of plasmids of six of the later isolates of a large band which was present in the digest of the plasmid from one of the earliest isolates of *K. pneumoniae* API 5205773 (transconjugant 1) may represent plasmid evolution during the outbreak. Whether a similar process could account for the greater differences in the plasmid from the *Citrobacter* isolate (transconjugant 8) is uncertain. In support of its being related are the bands it has in common with the other plasmids and the fact that it was isolated from a patient who also had gentamicin-resistant isolates of a number of other species, including several of API 5205773. It is of interest that Datta and her colleagues found that the plasmid which differed most from

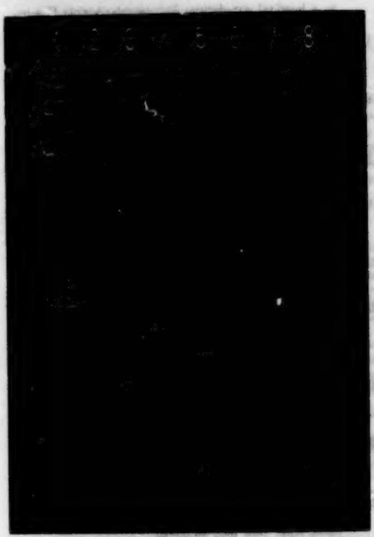

FIG. 4. *Agarose gel electrophoresis of EcoRI-digested fragments of plasmid DNA from the transconjugants described in Table 1, flanked on either side for reference by similar digests of λ phage.*

the others in the outbreak they studied was also from a *Citrobacter* (4), raising the question of host modification. There is no other evidence here that transposition may have contributed to the dissemination of the AAD (2″) gene, and it did not transpose experimentally, although the total number of both of these kinds of negative observation is small.

Although the previously rare AAD (2″) gene was the distinctive marker for this plasmid, it also carried genes for resistance to chloramphenicol, sulfonamides, and the TEM 1 β-lactamase gene. Since the latter two had been prevalent on other plasmids in the hospital and chloramphenicol, kanamycin, and tobramycin were seldom used there, gentamicin usage would seem to have been the most likely selective pressure for dissemination of the plasmid. Dissemination of the plasmid increased the prevalence of resistance to all of these agents and caused a more than threefold increase from 1976 to 1977 in the number of isolates of *Enterobacteriaceae* resistant to more than five antibacterial agents. The magnitude of this increase produced by one plasmid suggests that large differences between hospitals in prevalence of antibiotic resistance (14) might be accounted for by the circulation of a very few plasmids.

Restriction endonuclease analysis, mating experiments, and enzyme assay here confirmed dissemination of a plasmid after routine hospital laboratory results had already detected and traced it. Computer surveillance of clinical isolate files, including antibiotic inhibition zone measurements, could discriminate similar events in any hospital. Such observations in many hospitals might help to monitor and possibly to contain nosocomial or global spread of resistance genes (14, 16). These observations emphasize that resistance genes are too complex to arise often by chance mutation, so most strains of bacteria have to get them by transfer from other strains. Thus, the delivery of an antibiotic resistance gene through the world's bacterial flora to a strain exposed to that antibiotic may be as necessary for the emergence of resistance as is the antibiotic exposure.

The dissemination in patient flora of the plasmid described here is more extensive than that reported recently by Gerding (9) and Sadowski (18) and their colleagues, occurred initially in a different *K. pneumoniae* serotype (2 rather than 30), and ultimately became prevalent in another species, *S. marcescens*. The sequences of spread were similar, however, suggesting that there may be a stereotyped process through which a plasmid becomes disseminated in the patient flora of a hospital. Observation of additional plasmid incursions of this sort might further define the essentials of the process and suggest means for its prevention.

The plasmids involved in each of the outbreaks also seem similar. They are of approximately the same mass and appear to carry the same resistance genes. Moreover, although differences in method prevent direct comparison of the fragments, the two plasmids yield approximately the same number of fragments after *Eco*RI digestion. This raises the possibility that a resistance gene which spreads through the patient flora of a hospital on one plasmid may spread over a larger area or the whole world in the same way. It would be possible to detect and trace such a plasmid epidemic through computer surveillance of routine hospital laboratory files, as here, and confirm it with restriction endonuclease digestion analysis of plasmids selected by the surveillance.

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An Epidemic of Resistant *Salmonella* in a Nursery

Animal-to-Human Spread

Robert W. Lyons, MD, Cathryn L. Samples, MD, Hema N. DeSilva, MD,
Kathryn A. Ross, RN, Ernest M. Julian, RS, Patricia J. Checko, SM

• A *Salmonella heidelberg* epidemic in a hospital nursery was traced to infected calves on a dairy farm where the mother of the index patient lived. The *Salmonella* isolates from all cases were resistant to chloramphenicol, sulfamethoxazole, and tetracycline. Verification of the spread of infection from the farm animals to a hospital population is unusual and raises questions about the hazards of antibiotic animal-feed preparations that may induce infection with resistant organisms in humans.

(*JAMA* 243:546-547, 1980)

THE SPREAD of *Salmonella* from animals to humans is not unusual, and hospital epidemics of *Salmonella* are far from rare.[1] The occurrence, however, of a hospital epidemic with a multiple-drug-resistant *Salmonella* strain that had its origins in a herd of infected farm animals is remarkable.

Epidemic

On Aug 16, 1976, a shipment of calves arrived at a dairy farm in northern Connecticut. Several of these calves had diarrhea, and one died.

The farmer buried the calf himself and worked closely with the others. On Aug 20, mild diarrhea developed.

The farmer's daughter was pregnant and near term but continued to work on her father's farm until four days before delivery. She worked with the new calves, scooping milk from a bucket to each calf's mouth with her hand in an effort to teach them to feed from a bucket.

The woman was admitted to the hospital on Aug 24 because of irregular uterine contractions. Eighteen hours after rupture of fetal membranes, she was delivered of a full-term male infant by cesarean section. After delivery she experienced diarrhea but had had none before it.

A baby boy (infant 1), born on Aug 25, was well until Aug 28, when mild diarrhea developed, and his temperature rose to 38 °C. Blood and stool cultures were done, and his fever and diarrhea abated. The next day he had several loose stools, and fever again rose. He was then isolated.

A baby boy (infant 2), born Aug 26, was housed in the same nursery with infant 1. On Aug 30, infant 2 experienced diarrhea.

A baby girl (infant 3), born Aug 29, occupied a bassinet next to infant 1 for a few hours until infant 1 was isolated. On Aug 31, infant 3 experienced diarrhea and fever.

The blood culture of infant 1 and the stool cultures of all three babies and of the farmer's daughter grew *S heidelberg*, but all patients recovered without incident.

Patients and Methods

Investigation of Nursery.—The nursery is a 63-m square, has ten open bassinets, and has three wash sinks.

The average daily census is eight to nine infants who are full-term without identifiable risk factors and are cared for by two nurses per shift.

All three infected babies had been cared for by the same nurse. She recalled that while changing the diaper of infant 1 on Aug 29, she noted infant 3 to be choking. She rushed to the infant and aspirated mucus from the infant's pharynx; because of the acuteness of the problem, the nurse did not stop to wash her hands.

Stool cultures were performed on all infants in the nursery, all medical and nursing staff connected with the nursery, and the parents of the three affected infants. The nursery was closed to admissions until all infants present at the time of the outbreak were discharged.

Investigation of Farm.—The farmer's daughter lived with her husband in a house next to her father's farm. The woman reported that she had visited the farm daily Aug 16 through 21 to pet and feed her father's new calves.

A sanitarian from the State Health Department was sent to the farm to investigate.

Seventy veal calves younger than 1 week, bought at auctions in several different states, had been delivered to the farm on Aug 16. Several of the calves had diarrhea at the time of delivery, and several more experienced it during the next two to three weeks. One calf died on Aug 18, and another was returned to the seller. The farmer recalled that as many as 20% of the herd had been sick at one time or another, with several requiring intravenous therapy and treatment with oral nitrofurantoin, while others had responded to a simple change of feed.

Only three family members had close contact with the calves—the farmer, his son, and his daughter. All family members had stool cultures done. The farmer and his daughter had not had recent close contact or shared meals in the weeks before her admission.

The individual water supplies and sewage disposal systems serving the two family residences appeared satisfactory, as did the system serving the dairy barns and chicken coop. Cultures of the chicken coop and dairy barn manure were done.

Fecal cultures were done on seven calves from the herd with which the woman worked and also on seven calves from a herd purchased a week later. This latter herd had also experienced diarrhea.

Bacteriology.—Animal specimens and environmental cultures were done at the Connecticut State Department of Health laboratory. Human specimens were cultured at St Francis Hospital, and *Salmonella* isolates were forwarded to the Connecticut State Department of Health laboratory for confirmation.

Stool specimens were inoculated into Gram-negative broth (Scott) and plated directly onto 5% sheep blood agar, MacConkey agar, xylose, lysine, and desoxycholate agar. Plates were read after 24 hours' and 48 hours' incubation, and suspicious non-lactose-fermenting colonies were inoculated onto API 20 strips for identification. All plates were held for 48 hours before being reported as negative.

Serotyping of all specimens was done at the Connecticut State Department of Health laboratory using a variation of the method of Edwards and Ewing.[2]

Antibiotic sensitivity tests were done by the standard Kirby-Bauer method, and results were later confirmed by the Center for Disease Control by Mitchell L. Cohen, MD (written communication, September 1978).[3] Results are shown in the Table.

Results

The stool cultures from the woman and all three babies and the blood culture for infant 1 grew *S heidelberg* resistant to chloramphenicol, sulfamethoxazole, and tetracycline. The farmer's stool culture obtained on

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From the Department of Infectious Disease and Epidemiology (Dr Lyons) and Section on Neonatology (Dr DeSilva), St Francis Hospital (Ms Ross), Hartford, Conn; University of Connecticut, Storrs (Drs Lyons and DeSilva); Yale University, New Haven, Conn (Dr Lyons); and Field Services Division, Center for Disease Control, US Department of Health, Education, and Welfare (Dr Samples); Connecticut Department of Health (Mr Julian and Ms Checko), Hartford, Conn.

Reprint requests to St Francis Hospital and Medical Center, 114 Woodland St, Hartford, CT 06105 (Dr Lyons).

Antibiotic Resistance of *Salmonella heidelberg* Isolated From Calves and Patients

Source of Isolate	Resistance Pattern*						
Calf 1	Cmp.	Su.	Tc.	Nm.	Sm.	Km.	N
Calf 2	Cmp.	Su.	Tc.	Nm.	Sm.	Km.	N
Calf 3	Cmp.	Su.	Tc.	Nm.	Sm.	Km.	N
Farmer	Cmp.	Su.	Tc.	Nm.	Sm.	Km.	N
Farmer's daughter	Cmp.	Su.	Tc				
Infant 1	Cmp.	Su.	Tc				
Infant 2	Cmp.	Su.	Tc				
Infant 3	Cmp.	Su.	Tc				

*Cmp indicates chloramphenicol; Su, sulfamethoxazole; Tc, tetracycline; Nm, neomycin; Sm, streptomycin; Km, kanamycin; and N, nitrofurantoin.

Sept 8 grew *S heidelberg* resistant to those same three antibiotics and also to neomycin, streptomycin, kanamycin, and nitrofurantoin (Table).

None of the stools of the other persons cultured at the hospital or at the farm was positive for *Salmonella*.

None of the environmental cultures done at the farm was positive for *Salmonella*.

Stools from two of the seven calves from the first herd and one of seven calves from the second herd had *S heidelberg* with the same sensitivity pattern as that isolated from the farmer (Table).

Comment

We believe that this nursery epidemic originated in the dairy farm. The calves who came to the farm were infected, and the farmer and his daughter became infected while working with the animals. This infection presumably was by fecal-oral spread, although infected calves sometimes excrete *Salmonella* in their saliva.[4] Since the daughter was placing her hands in the calves' mouths, she could have acquired the organism from saliva.

Infant 1 is unlikely to have been infected at delivery, since his birth was by cesarean section. He might have been infected in utero during the 18 hours between membrane rupture and birth or on his one visit with his mother after birth before her infection became apparent.

The spread within the nursery is presumed to have been from infant 1 to the other two babies by way of the hands of attendants. In the case of infant 3, the aspiration done by a nurse who had just been handling the diaper of infant 1 seems likely to have been the critical incident. No such clear-cut episode emerged from the investigation of infant 2, but the same nurse was involved with his care, and some similar break in technique is not unlikely.

Introduction of *Salmonella* into a nursery and a subsequent epidemic has previously been traced to a child born of an infected mother.[5] In that case as in this one, the mother was asymptomatic at delivery. There seems to be no way to guard against such an occurrence, but alert and rapid response to illness in a nursery will help to limit spread.

Numerous reports have documented hospital epidemics of *Salmonella* infection. Nurseries for newborns seem especially liable to these epidemics. Twenty-two of the 112 institutional epidemics reported by Baine et al[1] in a survey from 1963 to 1972 occurred in nurseries. The frequent spread of the disease in nurseries suggests that the infecting dose in newborns is considerably less than the 10^6 organisms usually needed to infect adults.[6]

The animal source of this epidemic is unusual. Equally unusual is the antibiotic resistance pattern exhibited by the *Salmonella* isolates. These two unusual aspects may not be unrelated.

There has been concern that the use of antibiotics in animal feed might lead to antibiotic-resistant organisms in animals and that these organisms or their R factors could be transferred to human hosts.[7] The present epidemic is consistent with that hypothesis.

The finding of chloramphenicol resistance in all isolates in this epidemic serves to tie the isolates to a single source. Chloramphenicol resistance is distinctly uncommon among *Salmonella* strains in the United States. Two surveys of strains of various serotypes of *Salmonella* in 1973 showed less than 1% to be resistant, while a study in 1967 showed no resistance to chloramphenicol among 400 strains.[8-10]

In 1975, McHugh et al[11] reported an outbreak of three cases of chloramphenicol-resistant *S typhimurium* occurring on a burn unit in Boston. Chloramphenicol-resistant *S heidelberg* was responsible for a nosocomial epidemic involving nine patients in a New Jersey hospital reported in 1976.[12]

All strains isolated from the hospitalized patients showed resistance to three antibiotics. The strains isolated from the farmer and the calves showed resistance to these three antibiotics and also to four others. A simple explanation for this, which is consistent with our hypothesis of a single-source epidemic, is that the strain brought to the farm by the calves contained multiple R factors. In the process of transmission, one or more R factors was lost.

Studies on the mode of resistance of the organism have been conducted at the Center for Disease Control in Atlanta. Several patterns of resistance transfer were found among the strains of *S heidelberg* isolated, and this suggests the presence of more than one resistant plasmid (Mitchell L. Cohen, MD, written communication, September 1978).

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PUBLIC HEALTH SERVICE-CDC-Atlanta
EPI-77-13-2 July 1, 1977

TO : Director, Center for Disease Control

FROM : Bacterial Diseases Division and Field Services Division
Bureau of Epidemiology

SUBJECT: An Outbreak of Multiple-Drug Resistant *Salmonella heidelberg*, Connecticut

SUMMARY

An outbreak caused by multiple-drug resistant *Salmonella heidelberg* occurred in Connecticut in August 1976. The 5 known cases included 3 newborn infants in a hospital nursery, and the mother and grandfather of 1 of the newborn infants. The reservoir of infection may have been 1-week-old calves with salmonellosis owned by the grandfather. Transmission appears to have occurred directly from calves to persons in some cases and indirectly through person-to-person spread in others. Three of the 5 cases, all in infants, continued to excrete multiple-drug resistant *Salmonella* 10 weeks after infection.

Laboratory studies suggested that resistance was mediated through at least 2 transmissible R-plasmids. Preliminary observations did not demonstrate complete *in vivo* transfer of resistance from *Salmonella* to enteric flora. However, an R-plasmid mediating a rare pattern of resistance to multiple antibiotics appeared to have been indirectly transmitted from animals to 1 person. Further studies are in progress.

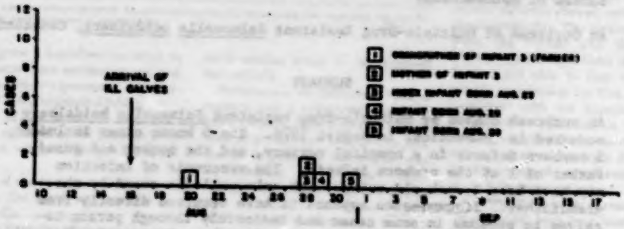
INTRODUCTION

On October 29, 1976, Cathryn L. Samples, M.D., EIS Officer located at the Connecticut State Department of Health, informed Mitchell L. Cohen, M.D., EIS Officer, Enteric Diseases Branch, Bacterial Diseases Division, Bureau of Epidemiology, CDC, of an outbreak of *Salmonella heidelberg* infection in Connecticut in late August and early September 1976. The organism was resistant to multiple antibiotics including chloramphenicol. After discussions between John V. Bennett, M.D., Director, Bacterial Diseases Division, Joy G. Wells, M.S., Chief, Enteric Diseases Laboratory Section, John Lewis, M.D., State Epidemiologist, Connecticut State Department of Health, Dr. Cohen, and Dr. Samples, Dr. Lewis concurred in CDC's providing assistance in further investigation of the outbreak. Accordingly, Dr. Cohen and Mrs. Wells departed Atlanta for Hartford on November 9.

A farmer (case 1) and his married daughter (case 2), resided in separate houses on a dairy farm in northern Connecticut. In August the farmer purchased seventy 3-5 day-old calves for veal from a central distributor. A number of these calves were ill with a diarrheal illness when they arrived on August 16. One calf died, and another was returned and destroyed.

The farmer's daughter, who was in her 9th month of pregnancy, assisted in the care of the calves from their arrival until August 21. On August 25 she gave birth to a boy (case 3) at a large Hartford hospital. On August 27, the mother developed fever and was started on ampicillin and gentamicin. On August 28 she developed diarrhea (Figure 1), and S. heidelberg was subsequently isolated from her stool cultures.

Fig. 1 CASES OF DIARRHEA IN PATIENTS WITH *SALMONELLA HEIDELBERG* INFECTION, BY ONSET, CONNECTICUT, AUGUST-SEPTEMBER 1976



The same day, her newborn became febrile and a gram-negative rod later identified as S. heidelberg was isolated from blood cultures. He was begun on ampicillin and gentamicin. On August 29 and 31, 2 additional infants (case 4 and case 5 respectively) who were cared for by the same nurse as case 3 developed diarrhea. S. heidelberg was isolated from stool cultures of both infants.

The Connecticut State Department of Health visited the farmer on September 8 and obtained stool cultures from him and 3 veal calves and environmental cultures, including manure from the dairy barn. When questioned, the farmer reported having had mild diarrhea beginning on August 20. S. heidelberg was isolated from stool cultures of the farmer and 3 calves. No pathogens were isolated from any environmental cultures.

All persons with S. heidelberg infection recovered without complications. In case 1, the man was treated with 10 days of ampicillin and gentamicin. In case 2, the mother was treated with a 4-6 week course of cephalexin.

For the first 6 weeks after arrival at the farm the calves were fed a routine formula containing bacitracin. In late September the feed was changed to a formula containing chlortetracycline.

INVESTIGATION

1. Materials and Methods

Histories of illness and antibiotic treatment since July 1, 1976, were obtained on the 5 cases, all household contacts, and controls. For each adult case, controls were selected from patients and employees of a Hartford hospital. Infant controls were selected from children attending a well-baby clinic at the same hospital. For cases that had received antibiotics, the control group included individuals who had received the same antibiotic at approximately the same time as the cases. If antibiotic-matched controls were unavailable, alternate controls who had received either chloramphenicol, tetracycline, or sulfoxazole were selected from hospitalized patients. Adult controls were matched for age within 10 years, and infant controls were matched within 6 months. After informed consent forms were completed, rectal swabs were obtained and plated directly as described below. Rectal swabs were also obtained on the 3 calves which had previously been identified as carrying S. heidelberg. Rectal swabs were directly plated to MacConkey's and MacConkey's containing chloramphenicol. An additional swab was placed in tetrathionate brilliant green broth. If present, 6 lactose-positive and 3 lactose-negative colonies were selected from each MacConkey and MacConkey chloramphenicol plate. The tetrathionate broths were streaked to brilliant green agar after 24- and 48-hours incubation. After a 24-hour incubation period of the plates colonies typical of Salmonella were picked and identified. Antibiotic susceptibility tests were performed on all isolates by the Kirby-Bauer method (12). Resistance transfer experiments were performed on both the original S. heidelberg and selected coliform bacteria isolated from cases and calves (3).

2. Results

a. Carriage of Salmonella

S. heidelberg was isolated from cases 3, 4, and 5, 10 weeks after infection. No S. heidelberg organisms were detected either directly or by enrichment from cases 1 and 2 or from any of the 3 calves.

b. Phage Typing

All isolates from this outbreak obtained from specimens submitted to the Connecticut State Department of Health were the same phage type.

c. Resistance of Salmonella

Two resistance patterns were identified in all isolates obtained from the Connecticut State Department of Health (Table 1).

Table 1. Antibiotic Resistances of Salmonella heidelberg Isolated by the Connecticut State Health Department from Calves and Patients, August - September 1976.

Source of Isolate	Resistance Pattern
Calf 1	Cmp, Su, Tc, Nm, Sm, Km, N
Calf 2	Cmp, Su, Tc, Nm, Sm, Km, N
Calf 3	Cmp, Su, Tc, Nm, Sm, Km, N
Case 1	Cmp, Su, Tc, Nm, Sm, Km, N
Case 2	Cmp, Su, Tc
Case 3	Cmp, Su, Tc
Case 4	Cmp, Su, Tc
Case 5	Cmp, Su, Tc

Note: Cmp = chloramphenicol; Su = sulfamethoxazole; Tc = Tetracycline; Nm = neomycin; Sm = Streptomycin; Km = kanamycin; N = nitrofurantoin

The isolates obtained from the 3 calves and the man (case 1) were resistant to chloramphenicol, streptomycin, sulfathiazole, tetracycline, neomycin, kanamycin, and nitrofurantoin. The isolates obtained from cases 2, 3, 4, and 5 were resistant to chloramphenicol, sulfathiazole, and tetracycline. Chloramphenicol, sulfathiazole, and tetracycline were conjugally transferred to a recipient organism at 37C from Salmonellae isolated from all 5 cases and the calves. Streptomycin, neomycin and kanamycin resistance as well as resistance to the above isolates from the calves and case 1 transferred at 25C.

S. heidelberg resistant to chloramphenicol, sulfathiazole and tetracycline was isolated from cases 3, 4, and 5 at the time of the study. *Salmonella heidelberg* isolates which were sensitive to multiple antibiotics tested were later recovered from all 3 cases. A third antibiotic resistance pattern which included resistance to chloramphenicol and sulfathiazole was identified in *S. heidelberg* isolates from case 4.

d. Resistances of Enteric Flora

Multiple drug resistant organisms were isolated from 10 of the 30 cultured individuals and from 3 of 3 calves (Table 2).

Table 2. Isolation of Multiple Drug-Resistant Coliform Bacteria

Group	No. of Individuals	No. with Multiply-Resistant Coliform Bacteria	No. of Multiply Resistant Isolates	Total No. of Isolates
Cases	5	2	5	33
Antibiotic treated	3	2	5	21
Untreated	2	0	0	12
Controls	18	7	42	132
Antibiotic treated	9	5	37	75
Untreated	9	2	5	57
Household Contacts	7	1	3	51
Calves	3	3	31	31
TOTAL	33	13	81	247

Eighty-one (33%) of 247 randomly selected colonies were multiple drug resistant (Table 2). Forty-two (44%) of 96 isolates from antibiotic treated cases and controls were resistant to multiple antibiotics compared with 5 (7%) of 69 isolates from individuals not treated with antibiotics; thus, isolation of a multiple drug resistant organism was associated with antibiotic usage ($p<.001$). All 31 calf isolates were resistant to multiple antibiotics. More multiple drug resistant isolates were identified in controls than cases, but the difference was not significant ($p=.083$). Antibiotic treated controls had significantly more multiple drug resistant isolates than antibiotic treated cases ($p=.047$). The proportion of multiple drug resistant organisms in household contacts, 3 (6%) of 51, was similar to the isolation in non-antibiotic treated controls, 5 (9%) of 59, ($p=.72$).

Twenty-one patterns were demonstrated among the 81 multiple-drug resistant isolates. Varying numbers of distinct patterns were demonstrated among calves (7), cases (1), controls (11), and household contacts (1). Only 1 pattern, resistance to streptomycin, sulfathiazole, tetracycline, ampicillin, neomycin, and kanamycin, was identified in isolates from both calves and humans. This resistance pattern was shared by *E. coli* from case 3 and 1 *E. coli* from each of 2 calves. These 3 isolates had the same resistance pattern and were non-typable *E. coli* with distinct biochemical reactions (Table 3).

Table 3. Biochemical Reactions of E. coli Isolated from 2 Calves and 1 Patient with Same Antibiotic Resistance Pattern

Source	Isolate Number	Sucrose	Salicin	Dulcitol	Raffinose	Rhamnose	Mucate	Lysine	Ornithine	Motility
Calf 1	1	-	Ag	-	-	AG	+	-	+	-
Calf 3	4	-	-	Ag	-	-	+	+	-	+*
Case 3	1	Ag	A	Ag	Ag	AG	-	+	+	-
Case 3	3	Ag	A	Ag	Ag	AG	-	+	+	-

*Serotype NAO.
A = Acid reaction
G = Definite gas production
g = questionable gas production

Two of 5 multiple drug resistant isolates from cases and 0 of 42 multiple drug resistant isolates from controls matched with multiple drug resistant isolates from calves; thus Salmonella infection was associated with isolation of a multiple drug resistant coliform bacteria that had the same resistance pattern as coliform bacteria isolated from calves ($p<.01$). This pattern of resistance was not identified in any of the 10,650 E. coli isolated from clinical sources from May through November 1976 and reported to the National Nosocomial Infections Survey by participating hospitals in the northeastern United States.

DISCUSSION

The evidence in this outbreak suggested the animal-to-man spread of a multiple antibiotic resistant S. heidelberg from ill calves to a farmer and his daughter. Subsequent person-to-person spread evidently occurred 1) from the mother to the infant at the time of birth, and 2) from infant to infant in the nursery where they were cared for by the same nurse. This outbreak emphasizes the danger to man posed by antibiotic resistant Salmonella from animal reservoirs.

Increasing antibiotic resistance among Salmonella serotypes has been documented repeatedly and poses a serious health problem. In 1968-69, 22% of Salmonella isolated at the Beth Israel Salmonella Center were resistant to 1 or more antibiotics (2); a survey at the same center in 1973 found 30% to be resistant (1). The resistance of S. typhimurium has been much higher than other serotypes (3). Of the S. heidelberg isolates sent to the Beth Israel Salmonella Center 10.5% were resistant in the period 1968-1969, but 30% of the isolates were resistant in 1973 (1). Fifty-one percent of S. heidelberg isolated in California during 1971-1972 were resistant to 2 or more antibiotics (4). Thus, serotypes other than S. typhimurium have become increasingly resistant.

The increase in resistance has not only involved commonly used agents such as tetracycline and ampicillin, but other drugs including chloramphenicol. Until recently chloramphenicol-resistant *Salmonella* isolates were unusual in the United States (3). In the California and Beth Israel surveys none of 691 and 7 (2.9%) of 241 *S. typhimurium* isolates were resistant to chloramphenicol respectively. However, at the Hospital for Sick Children in Toronto, Canada, 6 (12%) of 51 *S. typhimurium* isolates between 1973 and 1975 were resistant to chloramphenicol and ampicillin (5). Since 1975 chloramphenicol-resistant salmonellae have caused at least 5 outbreaks (5,6). In 1967 chloramphenicol was considered the drug of choice for the treatment of systemic salmonellosis, in the absence of sensitivity studies (3). The increasing number of outbreaks caused by chloramphenicol and ampicillin-resistant *Salmonella* not only challenges this recommendation but also poses a therapeutic dilemma.

Additional concern is that multiple drug resistant enterobacteriaceae, whether of animal or human origin, may donate resistance to pathogens such as *Salmonella*, *Shigella*, enterotoxigenic *E. coli*, and *S. typhi*. The increase in the number of antibiotic resistant *Salmonella* may reflect an increase in resistance of enterobacteriaceae, and the latter might have serious implications for the therapy of diseases other than systemic salmonellosis.

Controversy has continued over the significance of drug resistant coliform organisms that predominate in animals under the selective pressure of antibiotics in feeds. Two of the calves had *E. coli* with resistance patterns similar to the *Salmonella*. Since the initial antibiotic resistance of the *Salmonella* that infected the calves is unknown, any comments concerning the transfer of resistance between the calves' enteric flora and the *Salmonella* are speculative. However, the occurrence in a 2-1/2-month-old infant but not in controls of *E. coli* having the same rare resistance pattern but different biochemical reactions than the *E. coli* isolated from a calf suggests transmission of a calf-derived R-plasmid. The mechanism of transmission is not known. It is unlikely that the resistance pattern was acquired from the environment since none of the household contacts had this pattern. Also, the 2-1/2-month-old infant had no direct contact with the calves. Since this resistance pattern was associated with the *Salmonella* infection both the calf-derived R-plasmid and the *Salmonella* may have been transmitted from the mother to the baby during delivery. Early exposure of the baby to ampicillin may have contributed to the acquisition and carriage of the R-plasmid such an effect has been shown in experimental animals (7,8). The presence of R-plasmid in *E. coli* ingested by healthy adults, in the absence of exposure to antibiotics, has been shown to be detrimental (9) to the establishment of prolonged carriage. However, this experiment has not been performed in neonates who are establishing an enteric flora. This may explain why the plasmid was still present in the infant but not in the mother.

The temperature-dependent transfer of selected antibiotic resistance from the *Salmonella* to recipient *E. coli* suggests that resistance of *S. heidelberg* is mediated by at least 2 conjugative R-plasmids. The isolates from the farmer's daughter and 3 infants appear to have lost the R-determinants that confer kanamycin, streptomycin, neomycin, and nitrofurantoin resistance. In addition, some of the isolates from case 4 lost tetracycline resistance and all 3 infants had some isolates which were sensitive to multiple antibiotics. Thus, 4 different patterns of antibiotic susceptibility were identified in *Salmonella* isolates during the investigation. The most resistant organisms were isolated from the farmer who had received antibiotics and from the calves. The multiple drug sensitive strains were identified in infants who had carried the *Salmonellae* the longest; since R-plasmid carriage may be a selective disadvantage for the survival of *E. coli* in the human intestine in the absence of exposure to antibiotics (9), it is not surprising that persistent carriage in the infants was associated with the loss of resistance by a population of *S. heidelberg*. Coliform bacteria with resistance patterns identical to those of the *Salmonella* were not detected in cases or controls. *In vivo* transfer of R-plasmid from *E. coli* to *Salmonella* has been shown to occur in experimental animals (10,11) and is strongly suggested by observations in humans (3). The failure to demonstrate complete transfer of resistance from *Salmonella* to *E. coli* in this study may be the result of either sampling errors, incompatibility between the Salmonella and suitable recipient coliform bacteria, or less than optimal relative numbers of donors and recipient organisms. Longitudinal study of the infants with prolonged carriage is planned to evaluate these possibilities.

The study was originally designed to evaluate whether R-plasmid from Salmonella would transfer to endogenous flora of persons infected with the Salmonella. If so, this would provide proof that R-plasmid of animal origin could infect human endogenous flora under normal circumstances. However, observations made on E. coli in this study have strongly indicated that multiple drug resistant R-plasmids from E. coli of animals may be directly acquired by humans, by transfer of R-plasmid from E. coli animal strain to endogenous E. coli of humans. Thus, the study provides the first documented occurrence of direct acquisition of animal R-plasmids by human flora in conjunction with natural conditions of infection.

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Animal Model for Determining the No-Effect Level of an Antimicrobial Drug on Drug Resistance in the Lactose-Fermenting Enteric Flora

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Mature beagles were fed a ground-meal diet containing 0, 2, or 10 µg of oxytetracycline per g for 44 days. The 10-µg/g diet resulted in a shift from a predominantly drug-susceptible population of enteric lactose-fermenting organisms to a multiply antibiotic-resistant population which peaked at 78% resistant organisms. Since a shift to drug-resistant organisms did not occur in the group fed 2 µg/g, the level of oxytetracycline that results in increased incidence of antibiotic resistance lies between 2 and 10 µg/g in this dog model. Rats and hamsters fed diets containing oxytetracycline (10 µg/g or greater) or dihydrostreptomycin (10 µg/g), and provided suspensions of drug-susceptible *Escherichia coli*, did not develop a population of antibiotic-resistant organisms.

In a survey conducted in 1969, 5 to 43% of the livers and kidneys examined from cattle, swine, sheep, and chickens had antibiotic residues (6). Associated with these residues are potential toxicological (allergy or hypersensitivity) and microbiological health problems. The antimicrobial drugs which appear as residues in human food of animal origin have the potential of affecting the enteric microflora. From the standpoint of setting antimicrobial drug residue tolerance levels or determining acceptable analytical method sensitivities for detecting residues, it is important to consider the no-effect level of antimicrobial drugs on the drug resistance characteristics of enteric microorganisms, especially the *Enterobacteriaceae*.

The feeding of certain antimicrobials to chickens and swine results in a population of resistant lactose-fermenting enteric organisms. However, it may be difficult to obtain a source of these animals which have low enough baseline levels of resistant lactose-fermenting enteric organisms to give meaningful results. Guinea pigs are considered unacceptable because of their normal enteric flora (9). Because of the low numbers of *Escherichia coli* found in the enteric tract of rabbits (10), they, too, would likely be unacceptable.

In 1970 Guinee (4) reported that the addition of tetracycline (TC) to the diet of rats did not result in a buildup of drug-resistant *E. coli*. He also found that the addition of TC at 2, 5, and 10 µg/g to the diet of mice resulted in an increase in the recovery rate of an implanted resistant *Salmonella typhimurium* (3). This signifies that 2 µg of TC per g was enough to establish a selective advantage for the resistant *S. typhimurium*. TC fed at 10 µg/g in the diet of swine caused an increased incidence of resistant *E. coli* (5). The oral administration of oxytetracycline (OTC) to guinea pigs resulted in high concentrations of resistant *Proteus vulgaris* or *E. coli*, organisms which are not normally present in guinea pig feces (9). Thus, levels of antimicrobial drugs of 10 µg/g or less have affected enteric bacteria.

The present studies were conducted to find a suitable small animal model in which to determine the no-effect level of antimicrobial drugs on the drug resistance characteristics of the enteric flora.

MATERIALS AND METHODS

Dog experiment. Fifteen dogs (mature beagles) were divided into three experimental groups consisting of five animals per group. Each animal was maintained in a separate cage, and experimental groups were housed in separate buildings for the duration of the experiment. The animals were fed a ground-meal ration. Two treatment groups received meal supplemented with OTC at either 2 or 10 µg/g of diet continuously, whereas the control group was fed an antibiotic-free meal. Feed and water were provided ad libitum for 44 days.

Fecal samples were collected from each animal on three occasions prior to treatment and on days 1 through 10, 13, 15, 17, 21, 23, 30, 35, and 44 of the experiment. Samples were examined for resistant coliform organisms by a comparative plate-counting technique.

Rat experiment. Twelve mature albino rats were divided into four groups of three each and fed a ground laboratory diet. One group received antibiotic-free diet, and three groups received OTC-supplemented (10 μg/g) diets. All rats were fed continuously for 6 weeks. Additionally, a fresh suspension of drug-susceptible *E. coli* was added each day to the drinking water (10^8 organisms/ml) of one treatment group. To provide the rats with exposure to a greater variety of organisms than would normally be found in a clean-cage (not sterile) environment, or clean cage plus a single strain of *E. coli*, dirt which contained no *E. coli* was added to the cage of another treatment group. Organisms from the dirt resistant to dihydrostreptomycin (DSM), ampicillin (AP), TC, furazolidone, and sulfa were isolated from MacConkey agar plates. After 6 weeks the level of OTC in the diet of the three treatment groups was raised to 50 μg/g. Rats were fed this diet for 2 weeks. Feed and water were provided ad libitum.

Individual fecal samples were collected from rats at 1, 3, and 6 weeks after treatment with OTC at 10 μg/g of meal. Samples were also collected after the 2 weeks of treatment with OTC at 50 μg/g. Fecal samples (0.5 g) were used to determine the incidence of organisms resistant to either OTC (20 μg/ml) or DSM (20 μg/ml).

Hamster experiment. Two groups of six hamsters each were continuously fed a diet which was either antibiotic free (control) or supplemented with DSM at 10 μg/g. After 47 days OTC (10 μg/g) was also added to the diet, and a suspension of *E. coli* (10^8 organisms/ml) susceptible to the spectrum of drugs tested by the paper disk method was added to the water of one treatment group daily for 2 weeks.

Fecal samples were collected from each hamster two times prior to treatment and at 3, 12, 24, and 40 days after DSM was added to the diet. They were sampled again 2 weeks after the addition of OTC and the *E. coli* suspension. The incidence of lactose-fermenting enteric organisms resistant to either DSM (20 μg/ml) or OTC (25 μg/ml) was determined on 0.5 g of feces.

Microbiological methods. The total number of lactose-fermenting enteric organisms and lactose-fermenting enteric organisms resistant to OTC in the fecal samples was determined with an aerobic plating procedure utilizing phosphate buffer as a diluent. Tenfold dilutions of fecal material were plated on MacConkey agar plus OTC (20 μg/ml) or DSM (20 μg/ml). Counts of colonies which produced reactions and were morphologically characteristic of *E. coli* from both supplemented media were compared to the unsupplemented medium to calculate the relative percentage of OTC- or DSM-resistant organisms.

Three clones which produced reactions and were morphologically typical of *E. coli* were selected from unsupplemented media plates for each sample prior to treatment and on days 1, 17, 21, 23, 30, 36, and 44 of the dog experiment. Cultures were further tested on triple-sugar iron agar and Simmons citrate agar. Cultures giving reactions typical of *E. coli* were tested for susceptibility to AP, DSM (10 μg; in place of streptomycin), cephalothin, sulfamethoxypyridazine, colistin, chloramphenicol, furazolidone (100 μg in place of nitrofurantoin), neomycin, polymyxin B, TC, and nalidixic acid (NX). The disk technique of Bauer et al. (1) was used in this procedure.

Resistance transfer was determined on all isolates exhibiting TC and/or DSM resistance by a modification of the method of Schroeder et al. (8) utilizing an *E. coli* (K-12 F^-) mutated to a high NX resistance. Five media were used: MacConkey agar; MacConkey agar plus 25 μg of NX per ml; MacConkey agar plus 25 μg of NX, 10 μg of AP, and 10 μg of dicloxacillin per ml; MacConkey agar plus 25 μg of NX and 25 μg of DSM per ml; and MacConkey agar plus 25 μg of NX and 4 μg of TC per ml. The resistance of recipient clones was confirmed by the disk diffusion susceptibility test of Bauer et al. (1).

RESULTS

In fecal samples of dogs prior to treatment, the mean prevalence of lactose-fermenting enteric organisms resistant to OTC (20 μg/ml) was <1.0% for all three groups. In the group which received the 10-μg/g diet, the mean level of organisms in fecal material which was resistant to OTC rose to 5% by day 1 and to 20% by day 2 of treatment. Thereafter, the mean incidence of resistant organisms was never below 20%. After day 10 the mean incidence of resistant organisms remained above 40% except for two sampling intervals (days 30 and 44). A peak of 78% was attained on day 36.

At most sampling times for both the control group and the group fed 2 μg of OTC per g, the mean incidence of lactose-fermenting enteric organisms in the fecal specimens was <1.0%. At two sampling times for both the control (days 2 and 4) and 2-μg/g groups (days 1 and 15) the level of resistant organisms was >1.0%; peaks of 1.4 and 3.0% were attained by the control and 2-μg/g groups, respectively. At sampling on 12 and 13 occasions for the control and 2-μg/g groups, respectively, the mean incidence of resistant organisms was <0.1%. Many of these were below the limit of detection.

The five dogs fed 10 μg of OTC per g of meal did not respond to treatment at the same time or at the same rate (Table 1). In this group, the number of dogs which had undetectable levels of resistant lactose-fermenting enteric organisms decreased from the time treatment was initiated. Subsequent to day 13 all samples (one sample per dog per sampling interval) except two had an incidence of resistant enteric organisms of 10% or more. By day 2 of treatment, the incidence of resistant organisms was 100% in one dog. The incidence of drug resistance, in animals where resistance was detectable, did not go as high and occurred more slowly in the remaining animals. Through day 10, 37 of 49 total samples had detectable levels of resistant organisms. In 15 of the 37 samples the incidence of resistant organisms was <10%. Beyond 10 days the incidence of resistant organisms was >10% in 38 of 40 total samples.

During treatment, for the control and 2-µg/g groups, 85% of the total samples collected (one sample per dog per sampling interval) had undetectable levels of OTC-resistant organisms. Conversely, for the same period 13% of the samples collected from the 10-µg/g group had undetectable levels of resistant organisms. All of the 13% occurred during the first 10 days.

TABLE 1. Response of dogs fed OTC in diet

Day	OTC level (µg/g of meal)	No. of samples in which lactose-fermenting enteric organisms were resistant to OTC (20 µg/ml)					Total no. tested[b]
		Undetectable[a]		<1%[a]	1.0 to 10%	>10%	
		No.	%				
0	0	7	50	5	2	0	14
	2	8	57	4	2	0	14
	10	8	57	3	3	0	14
1-5	0	18	75	2	4	0	24
	2	21	84	3	1	0	25
	10	9	36	4	2	10	25
6-10	0	22	88	2	1	0	25
	2	25	100	0	0	0	25
	10	3	13	5	4	12	24
13-21	0	19	100	0	0	0	19
	2	14	78	2	1	1	18
	10	0	0	0	0	20	20
23-44	0	16	84	3	0	0	19
	2	15	75	2	2	0	20
	10	0	0	0	2	18	20

[a] Incidence of resistance.

[b] Samples were collected from five dogs per treatment group three times prior to day 0 on days 1/10, 13, 15, 17, 21, 23, 30, 35, and 44. One sample was collected from each dog per sampling time.

The predominant resistance pattern of the isolates obtained from the animals receiving the diet supplemented with OTC at 10 µg/g was DSM-TC (Table 2). Eighty isolates were multiply resistant, and four had a single resistance. Fifteen isolates were susceptible to the spectrum of drugs tested. Seventy-six and 74% of the DSM and TC resistances, respectively, were transferable. The AP resistances were 30% transferable.

In contrast to the isolates obtained from the 10-µg/g group, all nine resistant isolates obtained from the control group during treatment were singly resistant; 84 isolates were susceptible to the drugs tested. Similarly, seven of the isolates obtained from animals receiving a diet supplemented with OTC at 2 µg/g were singly resistant, and three were multiply resistant; 86 isolates were susceptible to the antibiotics tested. Most of the observed resistance in isolates from the control and 2-µg/g groups was transferable.

Resistant organisms were not recovered in either the rat or hamster experiments (Table 3). Providing the animals with a source of susceptible organisms was not sufficient to result in detectable levels of resistant organisms in fecal material.

DISCUSSION

Two prerequisites for a model system in which to determine the no-effect level of an antimicrobial drug on drug resistance in the aerobic enteric flora are low baseline levels of resistance to a spectrum of drugs and an animal system in which a response can be observed from use of a drug known to result in an increased number of pertinent organisms with drug resistance. In this study these criteria were met. The level of resistance to OTC in the lactose-fermenting enteric flora, as detected by the plate-counting procedure, was quite low and

TABLE 2. *Antibiotic resistances in lactose-fermenting enteric isolates obtained from dogs fed OTC*

Treatment period	OTC level (µg)	No. of isolates tested	Susceptible to antibiotics[a]	Antibiotic				
				AP	DSM	SU	TC	Other
Pretreatment	0	15	13	0	2	0	1	0
	2	13	11	0	3	3	0	0
	10	13	13	0	0	0	0	0
During treatment	0	93	84	0	4	0	1	4
	2	96	85	0	8	2	3	2
	10	98	15	14	81	16	80	6

[a] All isolates were tested with paper disks impregnated with the following antibiotics (one antibiotic per paper disk): AP (10 µg); DSM (10 µg); cephalothin (30 µg); sulfamethoxypyridazine (SU), (250 µg); colistin (10 µg); chloramphenicol (30 µg); furazolidone (100 µg); neomycin (30 µg); TC (30 µg); and NX (30 µg).

TABLE 3. *Emergence of antibiotic resistance in three animal species after feeding diets supplemented with either OTC or DSM*

Animal	Antibiotic/ diet (μg/g)	Days of treatment	Highest percentage of lactose-fermenting enteric organisms resistant to:[a]	
			OTC	DSM
Rat	OTC (10)	42	0	0
Rat	OTC (50)	14	0	
Hamster	DSM (10)	40		0
Hamster	OTC (10)	21	0	0
Dog	OTC (10)	44	78	
Dog	OTC (2)	44	3	

[a] Values are group means. Zeros indicate undetectable levels of lactose-fermenting enteric organisms resistant to the specified antibiotic. Pretreatment incidences of resistant organisms were <1.0% for the dogs.

remained so in the control animals. The incidence of TC resistance in the few isolates tested prior to treatment was also quite low. The incidence of resistance to DSM and sulfonamide in these isolates was higher than the incidence of resistance to TC, but low enough to detect changes.

The results indicate the no-effect level on drug resistance in lactose-fermenting enteric bacteria for OTC in the diet used in the dog model of this study lies between 2 and 10 μg/g. As can be observed in Table 1, length of exposure is related to magnitude of response in some animals, but a large response can occur in a very short time in other animals. This may be related to individual baseline levels of resistant organisms in the gastrointestinal tract or to genetic differences of the resident flora.

The lack of response in the animals fed the diet containing 2 μg of OTC per g may well be related to the minimal inhibitory concentrations of antibiotics on the organisms. It may also be related to drug absorption, drug inactivation (protein binding or chelation), drug stability, or dilution effects due to water consumption and internal secretions. Time may be another factor. Exposure over a much longer time may affect either the incidence of organisms resistant to TC or another drug such as DSM.

In determining the no-effect level of an antimicrobial on the enteric flora, homologous resistance to the drug being studied, as well as heterologous resistance, should be determined. In this study resistance to AP, DSM, and sulfonamide increased, as did resistance to the homologous drug. This aspect has been reported previously (2, 7), but the levels of drugs initiating the response were higher than those ordinarily found as residues in food.

This study confirms those previously reported (4) in that the oral administration of TC does not result in the emergence of a population of resistant *E. coli* in the rat. Even by adding a suspension of susceptible *E. coli* to the drinking water of the rats and hamsters, they both proved to be unsatisfactory as a small animal model for determining the no-effect level of an antimicrobial on the enteric flora. However, the particular strain of *E. coli* used in these studies may have been refractory to becoming drug resistant. In comparison, the dog model was found to be acceptable.

The no-effect level on drug resistance may vary among the various animal species in which a response to antimicrobials can be noted in the lactose-fermenting enteric flora. The dog model reported here is susceptible to at least 10 μg/g of diet (perhaps less) for OTC. Other animal species may be more susceptible. However, the availability of dogs with low baselines of resistant enteric organisms and their sensitivity for determining the no-effect level makes this model acceptable. This model is acceptable only for determining which antimicrobial drugs may produce an effect in the human if consumed as residues in food items. If human studies are considered necessary, the dog model may indicate the range of dose levels necessary. Due to species differences, direct extrapolation to humans should not be considered. Species differences may influence some drugs more than others.

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PUBLIC HEALTH ASPECTS OF ANTIBIOTIC-RESISTANT BACTERIA IN THE ENVIRONMENT

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This report is also available in French and Russian.

1. INTRODUCTION

In its long-term programme in environmental pollution control and in relation to its programme on hospital infections, the Regional Office for Europe of the World Health Organization, in collaboration with and sponsored by the Belgian Government, held a consultation on the public health aspects of antibiotic-resistant bacteria[1] in the environment. The main objective of the meeting was to consider the development of epidemiological surveillance and ecological studies of resistant bacteria. This had been recommended by a WHO Working Group on the Public Health Aspects of Antibiotics in Feedstuffs, held in Bremen, Federal Republic of Germany, from 1 to 5 October 1973.[2]

This consultation took the form of a hearing at which various national (Belgian) experts were invited, together with their senior and junior colleagues, to present the problem as seen by the different disciplines. There were eight sessions, at which a panel of four temporary advisers discussed the problem in turn with clinicians, microbiologists, veterinarians, food hygienists, ecologists, hydrobiologists, geneticists and public health administrators. A total of 38 scientists attended the various sessions. Two staff members of the WHO Regional Office for Europe and Headquarters were also present.

Stressing as it did the importance of a team approach at national and international levels for the review and study of such a ubiquitous problem, this consultation proved to be extremely rational in that a global problem could be examined by national research workers and administrators.

Dr A.H.W. Wahba, Regional Officer for Health Laboratory Services and Secretary of the consultation, opening the meeting on behalf of the Regional Director, Dr Leo A. Kaprio, said that the subject of antibiotic resistance needed a careful review in the light of recent increasing hospital and community epidemics. A coordinated monitoring system in which microbiologists and other relevant scientists would collaborate had to be developed. Professor A. Lafontaine, Director of the Institute of Hygiene and Epidemiology, welcomed the participants on behalf of the Belgian Government and expressed his satisfaction that the meeting was taking place at an institute where the problem of antibiotic resistance was receiving great attention.

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[1] The word "antibiotic" will be used throughout this report to include antibacterial drugs of natural or synthetic origin.

[2] World Health Organization, Regional Office for Europe (1974) The public health aspects of antibiotics in feedstuffs, Report on a Working Group, Bremen, 1-5 October 1973, Copenhagen

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2. CLINICAL ASPECTS OF DRUG RESISTANCE

Stress was laid on the predominance of infection by drug-resistant bacteria in specialized hospital units such as urological and paediatric units, burns and organ transplantation units, those for the intensive care of neurosurgical patients, and also, in some cases, in ordinary hospital units.

Drug-resistant bacteria responsible for infection change with time, and their resistance is related to the antibacterial drugs used. Methicillin-resistant *Staphylococcus*, gentamicin-resistant *Klebsiella* and *Pseudomonas aeruginosa*, and multiresistant *Serratia* have become increasingly prevalent in hospital practice.

Resistance among bacteria, and its spread, is generally the result of selective pressure of antibiotics. Resistant bacteria are transmitted between patients and resistance factors are transferred between bacteria, a phenomenon that occurs both in hospitals and outside.

It is difficult to assess precisely the magnitude of the problem, although it is undoubtedly very large and important. Unfortunately, data from all sources are incomplete. In practice, many infections, whether identified or not, are treated without bacteriological investigation. No data can be obtained from private laboratories which examine material from the majority of patients outside hospitals. These factors create epidemiological problems that impede proper scrutiny.

Different solutions have been proposed, such as:

(1) the prevention of such infections by the prophylactic use of antibiotics;

(2) treatment of infections with combinations of antibiotics (These practices are being increasingly regarded as counter-productive. They do not achieve their objective and add to the problem of drug resistance.);

(3) the prevention of spread of resistant organisms by the effective application of strict rules of hygiene, and by isolation where necessary. This is pre-eminently a hospital problem, to be correlated with the control of nosocomial infections.

It is therefore important that hospitals should maintain continuous surveillance and should report the prevalence of drug-resistant bacteria and of the infections they cause; the data obtained from different hospitals should be collated and transmitted to a reference centre to be retrieved.

The need has been recognized for the establishment of nosocomial infection committees within hospitals to carry out environmental surveys and to indicate appropriate control measures. Such committees should be supported by governmental regulations, including the provision of adequate staff and isolation facilities. Bacteriological and epidemiological information from different hospitals should be collated; the use of computers may be of advantage.

A regular reporting system should be established to indicate the prevalence of particular bacteria, their antibiotic susceptibility, the sites of infection and the hospital areas involved. Data from different hospitals using a common methodology would provide information for defining the extent of local or regional differences or similarities.

This basic knowledge might be supplemented by other bacteriological studies, carried out, if necessary, by specialized laboratories. The elucidation of the epidemiology of some antibiotic-resistant bacteria may require precise identification of the strains by phage-typing or the use of other markers.

A structure is therefore envisaged in which the clinical laboratory constitutes the primary source of information, e.g. on the resistance pattern of the organism which, together with the relevant bacteriological material, can then be referred to a laboratory with more extensive facilities. In this laboratory the primary genetic investigations in relation to possible transferability of the resistance can be carried out. The final stage in this framework requires the provision of a reference laboratory capable of studying the ecology and molecular epidemiology of the drug resistance. This would involve reference plasmids for comparative and compatibility studies. The organizational aspects of bacterial resistance surveillance are described in Section 7.

The drug-resistance of bacteria presents a real problem which cannot be resolved by the introduction of new antibiotics. A continuous programme of monitoring hospital-acquired infections, and of their prevention, should be recognized and promoted by public health administrations. The benefits that would accrue from such a programme would more than justify its cost by reducing, for example, the duration of hospitalization and expenditure on drugs.

Attention was drawn to the problems arising from the importation of "exotic" multiresistant Salmonella, which could cause serious difficulties in the population at large and in hospitals. The study of such strains, in order to identify distinctive features that could facilitate their recognition, might require the extraction and characterization of their plasmid DNA; in effect, this is epidemiology carried to the molecular level.

Naturally, this type of study should be extended to whatever resistant bacteria may be prevalent in infection by the so-called "opportunistic" pathogens: Klebsiella, Pseudomonas, Serratia, Proteus, and also

Staphylococcus, though the plasmid identification is not so precise in the staphylococci as in the gram-negative rods.

An example of the rise in incidence and importance of an opportunist pathogen is the increase of infection, sometimes fatal, by multiresistant *Serratia marcescens* in many countries during the past decade.

3. MICROBIOLOGICAL AND GENETIC ASPECTS

The historical aspects of the development of transferable drug resistance were dealt with in the report of the Working Group on the Public Health Aspects of Antibiotics in Feedstuffs.[1] Suffice it here to say that the phenomenon, demonstrated in Japan in the *Shigella* in 1959 and 1960, has now been demonstrated in all the enterobacteria, including non-pathogenic *Escherichia coli* of all known and many uncharacterized varieties. It has been found in many *Shigella* strains outside Japan, including the *Sh. dysenteriae* type I which caused the immense outbreak in Central America and which is believed to have caused over 100 000 deaths from 1965 onwards; in the large Mexican typhoid outbreak which started in 1972 and produced many thousands of cases; with salmonellosis in animals and man in many parts of the world; with enteropathogenic *E. coli* in outbreaks of enteritis in young animals and human infants; and with exacerbations of infections with opportunist pathogens such as *Klebsiella*, *Pseudomonas*, *Proteus* and *Serratia* in many specialized, paediatric and geriatric intensive care units. Further details of some of these events will be found elsewhere in this report. In this section it is proposed to discuss the genetic structure of transferable resistance factors and the consequences of this structure.

Resistance (R) factors are transferable extrachromosomal genetic elements, or plasmids, in bacteria. They may code for single or multiple (as many as eight) resistances. Their resistance is directed against the antibacterial drugs used in human and veterinary medicine and in some countries also for growth promotion in livestock: pigs, poultry and cattle. The resistances concerned are those against the antibiotic penicillin - ampicillin (A), cephalosporins (Cx), chloramphenicol (C), gentamicin (G), neomycin-kanamycin (K), streptomycin (S), spectinomycin (Sp), and tetracyclines (T). Synthetic antibacterial drugs, such as the sulfonamides (Su) and trimethoprim (Tm) also elicit the corresponding transferable resistance.

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[1] See footnote 2, p. 1

It has similarly been ascertained that resistance to heavy metals such as mercury can be mediated by transferable resistance plasmids which may also code for multiple antibiotic resistance.

Resistance to furazolidine (Fu) and nalidixic acid (Nal) seems to be chromosomal in origin. However, if an organism carrying an R-factor also possesses Fu or Nal resistance, pressure by either of the latter drugs will select in favour of the R-factor. As with all transferable genetic agents, R-factors consist of DNA, and can be broadly divided into two classes (Anderson & Threlfall, 1974).

In class I R-factors, a genetic determinant for drug resistance (R-determinant) is integrated into the transfer factor (TF) which is responsible for its mobility, to form a single covalently-bonded plasmid which is transferred as an intact linkage group from donor to recipient bacteria. These recipients in turn become donors and can transfer the complete R-factor to new recipients. The transferability of the complex is usually stably retained. Class I R-factors may carry single or multiple resistances: though some resistances are easily lost, probably by deletion, others are stable. Loss of the transfer factor is usually associated with loss of the entire R-factor.

In class II R-factors, the resistance determinant and the transfer factor are separate plasmids, independent of each other in the host cell. They are apparently associated with each other only in transfer, although the nature of the association is as yet undetermined.

In class II transfer systems, a number of determinants may be independently associated with a single transfer factor in the host cell, and in the absence of multiple selection they are transferred independently to recipient strains. The resistances of the donor will thus segregate during transfer. Because of their independence, the R-determinants and transfer factors of class II systems can be lost individually.

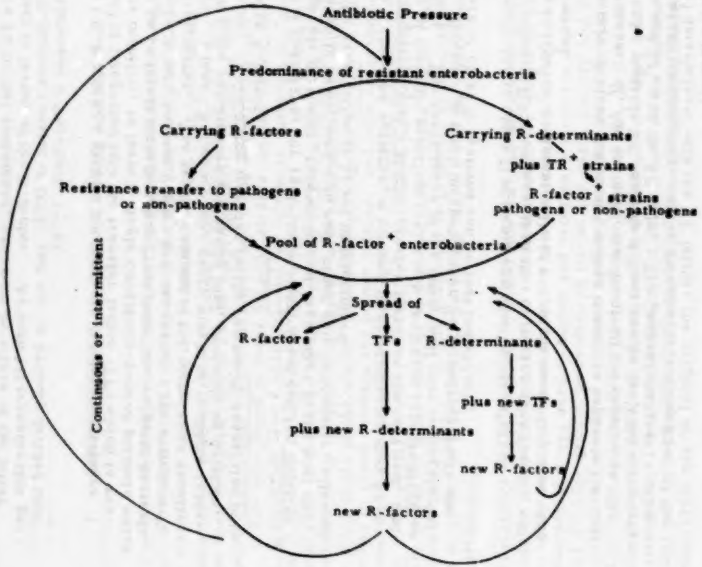
R-determinants in class II systems are usually transferred at a much lower frequency (10^{-2} or less) than that of the transfer factor, which may infect up to 100% of recipient cells in overnight incubation of mating mixtures (crosses).

The structure of class II systems makes it easy to separate the components in crosses. If, for example, the donor strain carries an SSu determinant and a suitable TF, recipient lines can be isolated that carry: SSu only, SSu and TF, and the TF only. The presence of the TF only, which yields sensitive progency, can be detected by mobilization of the SSu (or other) determinant with the TF (either the original or any other suitable transfer factor).

The ecological results of antibiotic pressure on the bacterial populations concerned can now be interpreted in terms of the genetic structure of R-factors, described above.

Fig. 1

THE R-FACTOR "CARROUSEL"


Antibiotic Pressure
Predominance of resistant enterobacteria
Carrying R-factors
Carrying R-determinants
plus TR⁺ strains
Resistance transfer to pathogens or non-pathogens
R-factor⁺ strains pathogens or non-pathogens
Pool of R-factor⁺ enterobacteria
Continuous or intermittent
Spread of
R-factors
TFs
R-determinants
plus new TFs
plus new R-determinants
new R-factors
new R-factors

The primary result of this pressure is the selection of resistant organisms, which may carry either complete class 1 or class 2 R-factors, or mobilizable R-determinants. The transfer of the former group, or the mobilization of the latter, results in the creation of a descendant pool of enterobacteria carrying R-factors (see fig. 1). Transfer occurs from this pool to other enterobacteria by the mechanisms shown, to increase still further the size of the pool. This pool will continue to increase in size even in the absence of antibiotics, but its enlargement will rise more steeply in their presence, because of the strong selection pressure they exercise. The point will ultimately be reached at which the transfer of resistance to pathogens becomes inevitable and the larger the pool, the greater is this probability. Moreover, the wider the distribution of R^+ enterobacteria, the greater the possibility that R-factors may emerge that can cross biological barriers, so that they can perhaps enter bacterial species and genera apparently widely different from their original enterobacterial hosts.

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Studies of the enterobacterial content of the intestinal tract of normal subjects have shown that over a period of about a year, all of more than 40 subjects, ranging in age from a few months to over 60 years, carried considerable numbers of clones of resistant *E. coli*, which sometimes constituted a majority of the coliform content of the intestine. Most individuals carried resistant *E. coli* at every examination. The resistance patterns varied frequently, and a particular sample could show a preponderance of organisms with resistance patterns unrelated to that of the previous sample, an indication that there was a change of the *E. coli* population of the individual concerned. Samples that carried no resistant *E. coli* were followed by others from the same person in which resistant organisms were present and vice versa. Resistance was usually multiple. The administration of short-term courses of antibiotics was sometimes followed by the emergence of organisms with the corresponding resistance, but this was by no means a constant finding. Persons suffering from conditions such as chronic bronchitis, and who were consequently on long-term courses of antibiotics, showed abundant *E. coli* carrying the corresponding resistances in their stools.

An important aspect of the acquisition of R-factors by pathogens is that the entire resistance spectrum, extending to as many as seven drugs, may be acquired in one or very few events. Since pathogens are invasive in their own right, and therefore need no selective support from the antibiotics to promote the infections they cause, a resistant pathogen with epidemic potentialities may spread widely in a susceptible human population in which it is disseminated by its normal epidemic routes. If one of the resistances it carries is directed against a drug that can be used in the treatment of the disease, that treatment then becomes ineffective. The disastrous outbreak of chloramphenicol-resistant typhoid in Mexico is an excellent illustration of these points. Only one strain of the typhoid bacillus was involved, and the R-factor concerned, which had the resistance spectrum CSSuT, was transferred to it as a single linkage group, that is, in one event. The entire outbreak, involving some thousands of

deaths, was thus caused by a single line of the typhoid bacillus, which needed only one R-factor transfer and the opportunity of epidemic spread to cause the largest and most troublesome typhoid outbreak on record. Many analogous examples can be cited, and the appearance of plasmid-mediated drug resistance in genera such as Vibrio, Haemophilus, Clostridium, Streptococcus and other organisms widely different from the enterobacteria, may be a hint that R-factors have greater transfer potentialities than was previously thought.

4. VETERINARY ASPECTS

The use of antibiotics in veterinary medicine, with the resulting emergence of resistant bacteria, was considered under three main headings: prophylaxis, treatment and use as feed additives. As the latter use is on a much wider scale than the two former, it will be considered first.

The supplementation of animal feeds with antibiotics to promote growth dates from the late 1940s, and became widespread from the early 1950s onwards. The drugs are added in low concentration, about 5 to 20 parts per million (ppm) commonest range, although this could rise to as high as 100 ppm. The commonest drugs used have been penicillin and tetracyclines; the latter have dominated the field. The mechanism by which growth is promoted remains obscure, but there seems to be little doubt of its efficacy, at least in the early period of its use.

It was soon established that the use of tetracyclines as feed additives, even in concentrations as low as 3 ppm, led to the emergence of tetracycline-resistant E. coli; this was observed in 1957, and it is now known that the resistance that appears is transferable.

Although these antibiotics were used as feed additives, the influence of tetracyclines on the emergence of resistance was probably the greatest and it also endowed the affected enterobacteria with the potentiality to acquire other resistances by mechanisms described in the section on microbiological and genetic aspects.

The development of intensive farming methods for the mass production of animal protein has created many problems. One of the most significant of these has been the susceptibility to large-scale infection of the animal population concerned because of low standards of hygiene, overcrowding and bad husbandry in general. Once an epidemic pathogen is introduced into such a population, it spreads rapidly, so that the entire herd may be infected. The conditions of intensive farming are such that preventive methods of isolation and practical hygiene are difficult to apply effectively. The practice was thus adopted of blanketing the entire herd

with prophylactic antibiotics in order to prevent and control infection. Ampicillin, for example, was widely used in England from 1964 onwards to control the spread of infectious diarrhoea caused by Salmonella typhimurium in intensive calf-rearing units. There is no evidence to suggest that the drug was effective in this respect, but transferable resistance against it rapidly appeared in the single strain of S. typhimurium Type 29 that caused the epidemic. Treatment of the infected animals with therapeutic doses of the drug was ineffective for the same reason, and the disease rapidly spread throughout Britain because of the distribution of infected calves by a single dealer. As a result of this and similar incidents, several committees were set up in various countries to examine the situation and make recommendations. These consisted mainly in the withdrawal of certain "therapeutic" antibiotics from use as animal feeding stuffs, more effective hygiene instruction for veterinary personnel and the establishment of a veterinary public health infrastructure and practice.

It is encouraging to note that the European Economic Community is developing and continuously revising regulations for the use of antibiotics in animal feeds. The present trend is to reduce the number of accepted antibiotics as well as their concentration.

5. ECOLOGICAL ASPECTS

Bacteria resistant to antibiotics and chemical drugs in general, can be distributed in the environment in different ways:

(a) the discharge of raw or insufficiently treated domestic sewage in surface waters, sea-water and on the soil;

(b) the discharge of raw animal wastes in aquatic biotopes or on the soil; pollution of surface waters by non-disinfected effluents from animal waste treatment plants;

(c) the distribution of activated sludge produced in domestic sewage purification plants and by systems for the purification of semi-solid animal wastes;

(d) the propagation by air from large industrial poultry and animal production units.

The importance of R$^+$ enterobacteria as a source of antibiotic resistance plasmids in human and non-human pathogens was established in the preceding sections. In Salmonella, the resistance may be acquired in animals, as happened in the S. typhimurium Type 29 outbreak in the

United Kingdom, or in man, as has apparently happened in lethal outbreaks of salmonellosis, especially in paediatric units, in many parts of the world. The chloramphenical-resistant typhoid outbreak in Mexico and the resistance to chloramphenicol in over 80% of cases of tyhpoid fever in South Viet-Nam by the spring of 1975, are examples of the conversion of a specific human pathogen to resistance in man as a result of the immoderate use of antibiotics.

All R-factors belonging to the same compatibility groups, of human or animal origin, have recently been shown to be clearly similar, if not indistinguishable, in all properties, including that of deoxyribonucleic acid structure. There is thus no reason to distinguish between transferable resistance of human origin and that of animal origin. Man is incidently exposed to the acquisition of R^+ enterobacteria arising from the use of antibiotics in animal rearing and in medicine. The distribution of these bacteria is now so wide in the general environment that it is no longer necessary to attempt to relate their appearance in the individual to the use of the antibiotics concerned. It is their use in the community as a whole that is now the overriding influence, and it is only by applying communal measures that there can be any hope of rectifying the situation, though it has now advanced so far that it is debatable whether it can be repaired. Nevertheless, the call for reform in the use of antibiotics may prevent the extension of an already serious problem.

The group proposed extensive studies, including those of sewage, surface water, soil, air and of other environmental sites, in order to clarify the avenues of distribution of R^+ bacteria.

6. ADMINISTRATIVE ASPECTS

It emerged from the discussion that full control over the production, importation, distribution and use of all antibacterial substances for human, veterinary and nonmedical use should be exercised by the relevant authorities. The promotional campaigns of manufacturers of antibacterial drugs require critical appraisal. Similar standards of purity, safety and pharmacological activity and labelling of all antibacterial drugs should be required. Continuous quality control should be exercised over all these products. It might be advisable to restrict the use of certain antibacterial drugs to hospitals. The inclusion of antibacterial substances in human foodstuffs and cosmetics should be prohibited. The recommendations of the 1973 WHO Working Group in Bremen[1] should be implemented.

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[1] See footnote 2, p. 1

Drugs that are therapeutically useful, actually or potentially, should be excluded from use as animal feed-additives.

It was noted that the withdrawal of antibiotics for animal feeds might result in an increase of prescriptions for the relevant drugs which could be added to feeds in higher concentrations than those permitted by regulation for normal feeds.

It was considered vital that all scientific information should immediately be made available to all bodies concerned so that effective action might be taken.

7. SURVEILLANCE OF BACTERIAL RESISTANCE - ORGANIZATIONAL ASPECTS

Apart from the essential lines of research approaches mentioned in section 8, it is of primordial importance to develop surveillance of bacterial resistance at national and international levels.

It is therefore proposed that in each country or area within a country, a laboratory specially concerned with antibiotic resistance problems should be given a reference status, so that it can organize surveillance activities. The terms of reference of this laboratory will include the setting up of a network of laboratories at two different levels. The first level will include clinical bacteriological laboratories attached to hospitals where the results observed in daily routine antibiotic sensitivity tests are collated and reported to the second level laboratories. The latter have epidemiological and ecological functions and are thus able to interpret results and proceed with more detailed enquiries and techniques. Standardized methods for sensitivity testing have been recommended (Ericsson & Sherris, 1971).

The three types of laboratory for clinical bacteriology, for reference and for epidemiology, will represent three levels of technological development from the simple antibiotic resistance pattern determination, through genetic studies of the responsible plasmids to the physioclinical studies of their deoxyribonucleic acid.

The national networks described should be linked with an international bacterial resistance surveillance programme, a prerequisite for which is the use of certain generally accepted methods of study, allowing comparable results to be obtained. The details of such a methodology could be worked out by a scientific group which, apart from geneticists and molecular epidemiologists in the field of plasmids, would include clinical bacteriologists, epidemiologists and statisticians. This group would have to deal with four procedural problems:

(a) The system of sampling the strains to be considered originating from human (infections with or without symptoms, carrier states), animal and environmental sources. At the same time, guidelines for following hospital infection incidences into the general community must be worked out.

(b) The techniques for measuring the resistance as well as the numeration of resistant bacteria in the natural flora should be sufficiently defined.

(c) The expression of the various results will need standardization. This may present certain difficulties: if it is easy to study the evolution of resistance of a pathogenic bacterium causing a specific infectious disease, it appears much more difficult to specify a pollution index of a natural flora by resistant bacteria.

(d) The establishment of an expert group in the form of a standing advisory committee, whose duties will be to examine new evidence of resistance and to evaluate the progress of such resistance.

All information on the evolution of bacterial resistance and, in particular, on the appearance of new resistance characters in a certain country or region is of the greatest value to the treating physicians in view of the grave therapeutic consequences. All possible channels for the diffusion of such information should therefore be fully used.

5. GENERAL CONCLUSIONS AND RECOMMENDATIONS FOR FURTHER ACTION AND RESEARCH

1. In relation to the emergence of bacteria possessing resistance factors (R^+ bacteria), there is a need for much more precise information on how animal growth is promoted by using antibiotics as feed additives. If used in the amounts hitherto permitted, are these additives still maintaining their efficiency in boosting growth? There is a lack of up-to-date information on this subject.

2. Exploration is needed of the possible role of food and animal feeds in the dissemination of R^+ bacteria.

3. There is a continuing need to study all the chemical, biological and physical factors that may possibly affect the presence of R^+ bacteria in

ıe environment: heavy metals, organic chemicals liable to be present in :ctory and domestic wastes, disinfectants, detergents, etc.

Environmental fields requiring investigation and possible control :tivities in relation to the presence therein of R^+ bacteria are:

(a) surface waters;

(b) sewage and wastes from possible areas of high concentration of R^+ bacteria, such as effluents from abattoirs, animal-rearing units and processing plants;

(c) surface contamination, such as that of vegetation and grass;

(d) soil, sludge;

(e) air in buildings used for livestock-rearing on an industrial scale;

(f) wildlife.

Such investigations would require the collaboration of microbiologists om the relevant fields, together with other specialists.

Sewage and surface waters should be examined for the possible :esence of plasmid-specific bacteriophages and a potential link between :is and the presence of the corresponding plasmids in bacteria.

. In hospitals or similar self-contained environments, opportunistic ıthogens may need the selective support of antibiotics for the promotion f the infections they cause. When the selective support factor is removed, ıe infections tend to abate. It may therefore be advisable to arrange for ıe temporary withdrawal of antibiotics from affected wards or institutions. t may also prove necessary to limit the use of some others, especially ıew antibiotics, to hospitals only where they will be used for specific, vell-defined conditions.

7. The possible role of cytotoxic and antimitotic drugs in the emergence of transferable resistance should be examined.

8. Medical students, physicians and other health personnel, as well as veterinarians, pharmacists, nurses and agricultural specialists should be trained to recognize the dangers of indiscriminate use of antibiotics. Information on the subject should be made available to the medical bodies concerned. It is desirable that all governments should insist on the supply of therapeutically useful antibiotics to the public only on prescription.

9. It is essential to develop immunological approaches to the problem of infection caused by antibiotic-resistant organisms. There should be support for the development of vaccines against Pseudomonas, Klebsiella and Serratia.

10. It would be informative to mount a study in areas where antibiotics are not known to have been used, to detect the possible presence of plasmid-mediated resistance in enterobacteria.

11. Research should be conducted into the mechanism of plasmid-mediated resistance to antibiotics, with the object of developing simple and practical techniques for identifying the genes involved in such resistance.

12. Collaborating laboratories for reference surveillance and research in the field of bacterial resistance should be established at national levels. International collaboration between such laboratories should be facilitated. Their role in national surveillance programmes could be further extended at a proposed meeting at WHO Headquarters in 1977.

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PROGRAMME

Tuesday, 9 December

9.00	**Registration of temporary advisers**
9.15	**Introduction - Professor A. Lafontaine**
	Scope and purpose - Dr A.H.W. Wahba
11.00	**Clinical aspects of antibiotic resistance - Dr E. Yourassowsky**
	Discussion
14.00	**Antibiotic resistance and the public health administration - Professor A. Lafontaine**
16.00	**Temporary advisers' conclusions** **- Professor E.S. Anderson** **- Professor Y.A. Chabbert** **- Professor E. van Oye**

Wednesday, 10 December

9.00	Microbiological aspects of antibiotic resistance - Professor J. Vandepitte
	Discussion
14.00	Antibiotic resistance in veterinary medicine and food hygiene - Dr P. Pohl
	Discussion
16.00	Temporary advisers' conclusions

Thursday, 11 December

9.00	Hydrobiological aspects of antibiotic resistance - Professor J. Voets
	Discussion

Thursday, 11 December (contd)

11.00	**Ecological aspects of antibiotic resistance** **- Professor J. Schell**
	Discussion
14.00	**Genetics and antibiotic resistance** **- Professor P. Fredericq**
	Discussion
16.00	**Temporary advisers' conclusions**

Friday, 12 December

9.00	**Presentation and discussion of the report**

ANNEX III

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Annex III

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Medical Officer, Bacterial Diseases

This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization

Surveillance for the prevention and control of health hazards due to antibiotic-resistant enterobacteria

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Report of a WHO Meeting

World Health Organization
Technical Report Series
624

World Health Organization Geneva 1978

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WHO MEETING ON SURVEILLANCE FOR THE PREVENTION AND CONTROL OF HEALTH HAZARDS DUE TO ANTIBIOTIC-RESISTANT ENTEROBACTERIA

Geneva, 18–24 October 1977

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SURVEILLANCE FOR THE PREVENTION AND CONTROL OF HEALTH HAZARDS DUE TO ANTIBIOTIC-RESISTANT ENTEROBACTERIA

Report of a WHO Meeting

A WHO Meeting on Surveillance for the Prevention and Control of Health Hazards due to Antibiotic-resistant Enterobacteria was held in Geneva from 18 to 24 October 1977. The Meeting was opened on behalf of the Director-General by Dr A. Zahra, Director, Division of Communicable Diseases.

1. INTRODUCTION

The World Health Organization has taken an active interest in the problem of antibiotic resistance. In 1960 a first attempt was made to standardize the laboratory test for determining susceptibility (*1*), although it was only in 1976 that the WHO Expert Committee on Biological Standardization drew up requirements for antibiotic susceptibility tests using the disc method (Requirements for Biological Substances No. 26) (*2*). In the meantime, the public health aspects of antibiotics in foodstuffs and in the environment were examined by three WHO expert committees (*3–5*) and by two meetings organized by the WHO Regional Office for Europe.[1], [2] In 1974, a WHO Collaborating Centre for Research and Reference Services for Biological Products, in Particular Antibiotics and Antibiotic Substances, was established in Atlanta, GA, USA, and in 1975 the WHO Collaborating Centre for Reference and Research on Enteric Phage-typing at the Enteric Reference Laboratory, London, England, expanded its terms of reference to include international studies on antibiotic resistance in enterobacteria.

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[1] WHO Regional Office for Europe. *The public health aspects of antibiotics in feedstuffs. Report on a Working Group, Bremen, 1–5 October 1973*, Copenhagen, 1974 (unpublished document EURO 3604 (2)).

[2] WHO Regional Office for Europe. *The public health aspects of antibiotic-resistant bacteria in the environment. Report on a Consultation Meeting, Brussels, 9–12 December 1975*, Copenhagen, 1976 (unpublished document ICP/FSP 002).

Outbreaks of infection due to drug-resistant organisms are an increasing problem in both the developing and the developed countries. This problem has been brought into prominence by the recent widespread outbreaks of enteric diseases caused by drug-resistant organisms; delayed recognition of drug resistance has, on several occasions, caused unnecessary suffering and loss of life. An equally serious problem is that of nosocomial infections with drug-resistant opportunistic pathogens of intestinal origin which invade the bloodstream, surgical wounds, the urinary tract and other tissues, particularly in enfeebled hosts. The problem is global and is the result of the widespread and indiscriminate use of antimicrobial drugs in man and animals.

There is a need for more rational and coordinated administration of antibiotics and for strict measures against their abuse. Uncontrolled and excessive use of antibiotics in man and animals results in an increase in antibiotic resistance and diminishes the effectiveness of these life-saving drugs. The problem is a man-made one and could be mitigated if agreement were reached on a more rational approach to the use of antibiotics. Unfortunately, current practices and the limited awareness both of health administrations and of the general public make such an approach difficult to adopt.

The Meeting was convened to review the current problems caused by antibiotic resistance among the enterobacteria and related organisms on a worldwide basis, and the factors involved in the spread of resistant organisms. The participants also reviewed methods of surveillance of resistance in enterobacteria and recommended simple methods whose operation would generate internationally comparable data. This could facilitate the appropriate use of antibiotics and permit early recognition of epidemics caused by resistant bacteria, so that control measures could be rapidly applied. The objective was to promote the development of national and international policies for antibiotic use.

This report summarizes the present state of the problem and proposes action which the participants considered might be feasible and effective for reducing the frequency and ill effects of antibiotic resistance in the enterobacteria.

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3. WHO Technical Report Series, No. 260, 1963 (*The public health aspects of the use of antibiotics in food and feedstuffs* : Report of a WHO Expert Committee).

4. WHO Technical Report Series, No. 430, 1969 (*Specifications for the identity and purity of food additives and their toxicological evaluation : some antibiotics* : Twelfth report of the Joint FAO/WHO Expert Committee on Food Additives).

5. WHO Technical Report Series, No. 598, 1976 (*Microbiological aspects of food hygiene* : Report of a WHO Expert Committee with the participation of FAO).

2. EXPLANATION OF CERTAIN TERMS

The term "resistance" is used to describe several different phenomena, and the following explanations provide more precise descriptions.

2.1 Antibiotic resistance *in vitro*

A susceptible strain is one that is consistently inhibited by a particular low concentration of a given antibiotic. An organism is resistant when it tolerates a concentration of antibiotic significantly higher than that which inhibits the growth of susceptible strains of the same species *in vitro*. *In vitro* predictions generally serve as a useful guide for clinical purposes, though the clinical outcome may sometimes vary for a number of reasons.

2.2 Natural resistance and acquired resistance

Some organisms are naturally resistant to antibiotics—for example, pseudomonads generally possess a barrier to the penetration of ampicillin and are therefore uniformly resistant. They are susceptible to carbenicillin but can acquire genetically the ability to produce an enzyme that inactivates the drug; this is an example of acquired resistance. Many other instances of natural resistance occur among the enterobacteria, such as that of most *Proteus* species to the tetracyclines and to colistin, of most *Klebsiella* to ampicillin, and of most *Enterobacter* to some cephalosporins.

2.3 Biochemical and genetic mechanisms of resistance

The biochemical mechanisms by which bacteria display resistance include the production of enzymes that destroy or modify the antibiotic, possession of a permeability barrier that prevents access to the bacterial cells, or alteration of the target site that is normally attacked by the antibiotic.

Genetic mechanisms by which bacteria acquire resistance include chromosomal mutation and also the acquisition of extrachromosomal elements (resistance plasmids). Plasmids code for a variety of characters and are now by far the major source of acquired antibiotic resistance in enterobacteria. They usually code for a high level of resistance, which may be multiple. The mechanisms of plasmid-mediated resistance are generally different from those of resistance of chromosomal origin ; the resistances to nalidixic acid and nitrofurans are of chromosomal origin, while those to other antibiotics are plasmidborne.

2.4 Abbreviations and definitions

For the sake of convenience, the following abbreviations of the names of antimicrobial agents are used in this report when reference is made to multiple resistance :

ampicillin	A	neomycin	N
amikacin	Ak	nitrofuran	Fu
benzylpenicillin	P	polymyxins	Po
carbenicillin	Cb	rifampicin	Ri
cephalosporins	Ce	sisomicin	Si
chloramphenicol	C	streptomycin	S
clindamycin	Cl	sulfonamides	Su
gentamicin	G	tetracyclines	T
kanamycin	K	tobramycin	To
nalidixic acid	Nx	trimethoprim	Tm

The word " antibiotic ", as used in this report, signifies all antibacterial drugs of natural or synthetic origin. The names of groups of antibiotics used in the text are aminoglycosides (gentamicin, kanamycin streptomycin), β-lactams (penicillins and cephalosporins) and macrolides (erythromycin, spiromycin and related compounds).

The term " enterobacteria " as used herein refers to Gram-negative aerobic rods found in the intestine which are members of the family Enterobacteriaceae.

3. PRESENT STATUS OF ANTIBIOTIC RESISTANCE IN ENTEROBACTERIA

3.1 Occurrence of antibiotic resistance in bacteria infecting man and animals

A search of the world literature, including a MEDLARS survey of literature on antibiotic resistance, highlighted the following points :

(1) There is a preponderance of reports on the occurrence of resistant strains in developed countries, and from investigators with a special interest in antibiotic resistance, and a shortage of information from the developing countries.

(2) In many countries there is a lack of standardization of methodology in the testing and reporting of bacterial resistance. This makes comparisons of information difficult.

(3) The time-span over which studies are made varies considerably—which is important because the situation may show considerable fluctuations with time; rapid changes may occur because of the emergence and spread of resistant strains.

However, allowing for the patchy distribution of the reported results and the variations in defining resistance, a few examples are quoted below to illustrate discernible trends.

3.1.1 Escherichia coli

Antibiotic-resistant strains of *E. coli* are prevalent in the general population of healthy individuals. For example, in the United Kingdom, about 15% of strains are resistant to ampicillin and 20% to streptomycin and/or the tetracyclines (*1*). In Japan, in 1974, tetracycline resistance was found in 70%, streptomycin resistance in 75%, and chloramphenicol resistance in 50% of isolates of *E. coli* from human sources. Multiresistant strains were also shown to be frequent in some areas: 12% of the isolates in Sweden in 1971 were resistant to ampicillin, chloramphenicol and tetracycline (*2*). No distinction has been made in this review between strains isolated from the community and those isolated in hospital. Moreover, attention should be directed to the patchy distribution of resistance that occurs within a country, which may be due to local predominance of a single resistant strain of *E. coli*.

The few studies that have been carried out on animal strains—for example, in the USA—show a very high prevalence of resistance, particularly to the tetracyclines (91% in pigs) and to streptomycin (94% in calves) (*3*). The low prevalence of resistant strains of *E. coli* in wild animals is an indication of the role that animal husbandry, especially the use of antibiotics in animal feeds, may play in producing the high isolation rate of resistant strains from livestock.

3.1.2 Shigella

Antibiotic resistance is very frequent in *Shigella*. For example, 90% of strains of *S. sonnei* in the United Kingdom were resistant to ampicillin in 1970 (*4*); 48–54% of strains of these shigellae were resistant to the tetracyclines and streptomycin in New York City, USA, in 1973 (*5*). Chloramphenicol resistance has not been a predominant feature in survey data, although epidemics have been caused by chloramphenicol-resistant strains. The prevalence of resistance in shigellae in Algeria (*6*), in developing countries of the Western Pacific,[1] and in Papua New Guinea (*7*) is reported to be considerably lower than in developed countries.

3.1.3 Salmonella

Considerable variation is found in the incidence of antibiotic resistance in salmonellae, particularly in multiresistant strains, in reports from different countries and, at times, from different areas of the same country (*8–10*). It was noted in a survey of animal strains that resistance was more prevalent in *S. typhimurium*, generally the commonest *Salmonella* serotype, than in other salmonellae. Isolated foci of resistance are also reported, such as the high incidence (90%) of streptomycin resistance in *S. dublin* in the Netherlands in 1971 (*11*). A large outbreak may, however, be caused by a single strain—i.e., a clone of one or more *Salmonella* serotypes—which makes it difficult to compare incidence in different areas or countries.

Information derived from data collected in the FAO/WHO Collaborating Centre for Research and Training in Food Hygiene, Berlin (West), emphasizes the variations in antibiotic resistance seen in salmonellae of animal origin. Over 1000 strains of salmonellae were examined each year from 1971 to 1976. Table 1 shows that during this period there was a rise and fall in resistance in *S. typhimurium*, a fall in resistance in *S. panama*, and a rise in resistance in *S. dublin*.

Tetracycline resistance in *Salmonella* in general remained at a constantly high level over the 6-year period and the use of tetracyclines as a feed additive was discontinued at the end of 1976. Resistance to chloramphenicol had risen to almost 50% and that to kanamycin to 25% by 1976. The association of these strains with infections in man in the Federal Republic of Germany remains unclear.

In the USA, overall resistance more than doubled in the period 1967–1975, the proportion of resistant strains rising from 22% to 50%.

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[1] Unpublished data.

Table 1

Variation in antibiotic resistance in *Salmonella* strains isolated from domestic animals in the Federal Republic of Germany

Serotype	Year of isolation					
	1971	1972	1973	1974	1975	1976
	Percentage resistant					
S. typhimurium	32	37	64	52	36	35
S. typhimurium (var. Copenhagen)	10	3	6	5	4	4
S. panama	65	58	52	22	6	2
S. dublin	3	1	7	16	70	70

Resistance in *S. typhimurium* increased 1.7 times and a greater increase, 2.8-fold, was seen in resistance of other serotypes. Multiple resistance increased significantly, from 15% to 26%, and the proportion of *Salmonella* strains with resistance to 6 or more antibiotics increased from 0.8% to 9.2%. As has been indicated, this may have been determined by the prevalence of a resistant clone, which could have been recognized by examination for genetic markers.

3.2 Outbreaks of human infection due to drug-resistant enterobacteria

Several types of infection may occur with antibiotic-resistant strains of enterobacteria—namely:

— shigellosis;

— typhoid fever;

— *Salmonella* enteritis associated with strains of animal origin;

— nosocomial infections with *Salmonella* species, particularly in neonatal and paediatric units;

— nosocomial infections of extraintestinal sites with other enterobacteria, such as *Klebsiella*, *Proteus*, *Serratia* and *Enterobacter*.

3.2.1 *Shigellosis*

Shigella dysenteriae type 1 (Shiga's bacillus), a highly virulent pathogen, caused an extensive outbreak that was first recognized in Guatemala and spread throughout Central America from 1968 to 1972. Severe bacillary dysentery affected hundreds of thousands or persons and caused tens of thousands of deaths (*12*). Disease caused by this antibiotic-resistant (CSSuT) strain was initially misdiagnosed as amoebiasis—partly because it did not respond to the antimicrobial drugs in common use; this delay in diagnosis contributed greatly to the formidable mortality. A widespread outbreak due to drug-resistant *S. dysenteriae* type 1 also occurred in Bangladesh, which persisted for several years; in 1973, 33% of the entire population of the island of St Martin in the Bay of Bengal was affected over a period of 3 months (*13*).

Infections with multiresistant strains of *S. sonnei* have been a persistent problem in many countries. For example, in the USA, 194 students and 14 staff members were involved in a waterborne outbreak due to a resistant (ASSuT) strain in a school in 1972 (*14*). In 1973, 12 cases with 2 deaths occurred at an institution for mentally retarded children; the responsible strains were resistant to AST (*15*). A high prevalence of ampicillin resistance in *S. sonnei* has been reported from many centres in the USA and elsewhere since 1967.

3.2.2 *Typhoid fever*

Although chloramphenicol-resistant *Salmonella typhi* had been described as early as 1950, the first recorded epidemic caused by a resistant strain occurred in Mexico in 1972–1973 (*16, 17*). This outbreak was due to a multiresistant (CSSuT) strain with a characteristic phage-typing pattern; the compatibility group to which the plasmid carrying chloramphenicol resistance belonged was designated H_1. The outbreak was unique, not only because it was caused by a drug-resistant strain, but also because of its long duration (over 2 years) and wide distribution (several states in central Mexico). There is no accurate record of the number of cases that occurred, but conservative estimates suggest that there were many thousands. The case-fatality rate early in this epidemic was similar to that experienced before the antibiotic era, but after it was determined that the organism was chloramphenicol-resistant, treatment with ampicillin is reported to have led to a dramatic reduction in the death rate.

In India, the first documented outbreak due to a resistance (R)-factor-carrying, multiresistant (CSSuT) strain of *S. typhi* (Vi phage type D1-N, later replaced by type C5 with the same resistance pattern) took place in Calicut (Kerala) in 1972 (*18*). The type C5 focus has persisted but has not spread widely. A localized outbreak occurred in 1976 at Ernakulam, about 20 kilometres south of Calicut, due to phage type A with the same CSSuT resistance pattern. This focus, too, has shown no tendency to spread (*19*). The plasmid responsible belonged in all cases to compatibility group H_1. Since then, outbreaks due to R-factor-carrying salmonellae of other serotypes have been reported from other parts of India. In 1976 single sporadic isolates were received from Trivandrum (Kerala), Madurai (Tamil Nadu) and Bombay (Maharashtra) (*19*).

In a study carried out by the Southeast Asian Medical Information Center, Tokyo, Japan, strains of *S. typhi* from 3 centres were compared : 87 from Singapore, 198 from Thailand and 390 from Japan. Resistance was not detected in Singapore, and in Japan it was at a very low level, while in Thailand 39% of the strains were resistant, the predominant pattern being CTS with A as an additional resistance in some cases. Antibiotic resistance in *S. paratyphi* A and *S. paratyphi* B was negligible. In Viet Nam about 80% of *S. typhi* strains were found to be resistant to many antibiotics (*20*, *21*). Information from Peru indicates that the proportion of strains of *S. typhi* susceptible to chloramphenicol fell from 90% in 1974 to below 30% in 1976 ; strains remained susceptible to ampicillin. Wherever chloramphenicol-resistant outbreaks of typhoid fever have been detected, the resistance has been mediated by plasmids of compatibility group H_1.

3.2.3 Salmonella *enteritis associated with strains of animal origin*

The drug-resistant strain of *S. typhimurium* that proved most important in early studies in the United Kingdom belonged to phage type 29, which first appeared in epidemic form in 1963–1964. It was found mostly in man and bovines, and its increased prevalence in 1963 coincided with the appearance of transferable resistance to streptomycin and the sulfonamides. Resistance to the tetracyclines became evident early in 1964, followed by that to ampicillin, chloramphenicol, furazolidone and neomycin-kanamycin in succession, while the frequency of the type greatly increased (*22*).

Studies of cultures from the United Kingdom and a number of other countries revealed that drug-resistant clones of *S. typhimurium* and other salmonellae were causing widespread outbreaks of infection, some on an international scale (*23*).

Two types of outbreak due to drug-resistant salmonellae (except *S. typhi*) have been identified : those which clearly have an animal origin and those in which no animal source can be identified. The first type is exemplified by the *S. typhimurium* outbreak in the United Kingdom, where the drug resistance is acquired in the animal host and the distribution is related to that of its animal source. The second type is commonly seen in paediatric units and is described in the following paragraphs.

3.2.4 *Nosocomial infections with* Salmonella *species*

In recent years, multiresistant salmonellae have caused many outbreaks. Morbidity and mortality have been especially great in paediatric units and nurseries.

In these outbreaks no animal source can be identified; they do not coincide with animal epidemics and the strains are not even present in livestock in the affected areas. The outbreaks appear quite suddenly; they are severe, with a morbidity rate of up to 50% and a case-fatality rate of up to 20–30%; septicaemia and meningitis are common. The infecting strain is almost always resistant to a multiplicity of drugs and may carry three or more plasmids.

Documented outbreaks have been associated with *S. typhimurium* (Argentina, Brazil, Chile, Paraguay, USA (Kentucky), and Uruguay), *S. heidelberg* (Puerto Rico), *S. newport* (India (Delhi) and Peru), *S. isangi* (Zaire), *S. virchow* (United Kingdom), *S. alachua* (India (Calcutta)), *S. wien* (Algeria, Belgium, France, Iraq, Italy, United Kingdom, and Yugoslavia). Nosocomial infection has featured prominently in the national spread of multiresistant strains of *S. typhimurium* in Argentina and Uruguay, *S. newport* in Peru, *S. isangi* in Zaire and *S. wien* in Iraq and countries of the Mediterranean region.

3.2.5 *Nosocomial infections with other drug-resistant enterobacteria*

During the past 20 years Gram-negative bacilli, particularly enterobacteria and pseudomonads, have been the most important agents causing hospital-acquired infections in many countries. Multiple resistance to antibiotics has been the rule in these infections.

Debilitated patients are easily colonized and subsequently infected by opportunistic Gram-negative bacilli, which may gain access to the body by way of intravascular catheters, bladder catheters, inhalation therapy devices, and respirators, or by other invasive techniques.

In 1970–1971 a protracted nationwide outbreak of septicaemia in the USA due to *Enterobacter cloacae* and *E. agglomerans* was traced to contaminated intravenous fluids (*24*). A similar episode occurred in the United Kingdom in 1973 (*25*); this was an outbreak due to *Citrobacter freundii* and *E. agglomerans*, also caused by contaminated intravenous fluid.

Most nosocomial outbreaks of infection are due to contact spread. A few examples of a very widespread phenomenon are cited here. One hundred and thirty cases of infection with *Proteus rettgeri*, with 5 cases of septicaemia and 1 death, were observed in a hospital in Memphis, TN, USA, in 1972. Twenty-eight patients in a hospital in Minneapolis, MN, USA, were infected or colonized with *Klebsiella pneumoniae* resistant to ACbCeCGKSu during 1976. Nosocomial outbreaks involving hundreds of cases of infection with strains of *Serratia marcescens* resistant to many antibiotics, including gentamicin and tobramycin, have been reported from other centres in recent years.

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4. RESISTANCE FACTOR SPREAD FROM ENTEROBACTERIA

During the past few years, it has been found that plasmidborne resistance may spread from enterobacteria to other bacterial species; some significant epidemiological events relating to other Gram-negative bacteria are listed below.

(1) *Pseudomonas aeruginosa*

In March 1969, Lowbury et al. (*1*) isolated from patients in a burns unit in Birmingham, England, strains of *Pseudomonas* that were highly resistant to carbenicillin through the production of β-lactamase. Subsequently, Sykes & Richmond (*2*) showed resistance transfer from these strains to *Escherichia coli* K12; the R factor concerned was designated RP_1. The resistance was linked to those of ATKCe and the same R factor was also found to be widespread in *Proteus* spp.

The appearance of gentamicin-resistant *Pseudomonas aeruginosa* strains reported by Witchitz & Chabbert (*3*) in France was a matter of considerable clinical concern. These strains had ACSu resistances which were transferred by conjugation to *E. coli* K12. R-factor-carrying strains isolated in the USA (*4*) were also resistant to the newer aminoglycosides, tobramycin and amikacin.

(2) *Haemophilus influenzae*

In 1974, cases of meningitis were reported that failed to respond to ampicillin because of resistance to that drug. The mechanism of resistance in some of these strains was shown to be due to a β-lactamase similar to the plasmid-mediated β-lactamase R_{TEM} (*5*).

Current prevalence of β-lactamase-producing strains in the United Kingdom remains at a fairly low level. Of 950 strains tested in early 1977, 14 (1.5%) were β-lactamase producing. However, there is some evidence that β-lactamase production is more likely to occur in the capsulated strains which cause the more serious infections, including meningitis, than in the noncapsulated variants. In the USA ampicillin-resistant strains of *H. influenzae* are responsible for 2–8% of serious infections caused by this organism.

(3) *Neisseria gonorrhoeae*

The acquisition of R factors by *N. gonorrhoeae* created widespread public health concern during 1976. Cases of penicillin-resistant gonorrhoea were observed in visistors or military personnel returning from countries of the Western Pacific area or West Africa to Europe and the USA (*6–8*). The production of β-lactamase by these strains was shown to be plasmid-mediated. Plasmids of two different sizes have been identified, and there is some evidence that the β-lactamase produced was the same as the β-lactamases of *H. influenzae* and enterobacteria (*9*).

(4) *Vibrio cholerae*

Resistance is very rarely seen in *V. cholerae*. However, some multiresistant strains have been described which can transfer their resistance by conjugation, thus confirming the plasmid-mediated nature of their resistance (*10*). These plasmids are generally unstable in *V. cholerae*, though a stable plasmid has been found in a few strains (*11*).

The above examples show that resistance plasmids can affect the ecology not only of the enterobacteria but also of other important pathogens. There is some evidence to support the hypothesis that the plasmids concerned are being derived from enterobacteria, which can share a habitat with other pathogens in clinical situations.

Two possible organisms that may be the next to acquire resistance plasmids are *Bacteroides* species and *Neisseria meningitidis*. The latter is normally distributed in the body in a fashion similar to that of *H. influenzae* and the occurrence of penicillin-resistant meningococcal meningitis would create enormous problems in the treatment of cases and the control of epidemics. The acquisition of β-lactamase by the related species *Branhamella catarrhalis* (*12*) is an indication that such drug resistance could well develop.

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5. FACTORS CONTRIBUTING TO THE EMERGENCE AND SPREAD OF ANTIBIOTIC RESISTANCE

5.1 Antibiotic use in man

The appearance of antibiotic-resistant strains of bacteria is closely linked to antibiotic use for the treatment of human infection (*1*, *2*). Resistance may appear rapidly or slowly, depending on the organism concerned, the volume and type of antibiotic used, and the method of application.

The most clear-cut reports of antibiotic use and resistance have resulted from hospital studies in which outbreaks of nosocomial infections were related to the extensive use of antibiotics. The following are examples: infections with *Klebsiella* related to the use of ampicillin in a neurosurgical unit (*3*), infections with pseudomonads resistant to carbenicillin in a burns unit (*4*), and resistant infections with *Serratia* associated with the use of gentamicin in an intensive care unit.

In community infections, data from Japan[1] and Poland clearly showed that a rise in tetracycline resistance in pneumococci was closely associated with an increase in tetracycline use. There was a sharp increase in macrolide use in Japan from 1967 onwards, the quantities administered having risen from about 50 000 kilograms a year to almost 200 000 kilograms a year by 1973. Macrolide-resistant strains of group A haemolytic streptococci were first recognized in Japan during the early 1970s and, by 1974, 75% of strains isolated were resistant to erythromycin and lincomycin. Resistance to the tetracyclines and that to chloramphenicol were at a level of 90% and 75% respectively. In a paediatric unit in Tokyo in 1963, all of 250 isolates of *Escherichia coli* showed CSSuT resistances. Since then, rises in antibiotic resistance have been observed with other agents as they have been introduced. An increase in ampicillin use occurred about 1964 and 27% of *E. coli* strains were resistant by 1969; an increase in the use of cephalosporin occurred in about 1972, and 31% of strains were resistant by 1975.

Unfortunately, precise data on antibiotic use in many countries are not widely available, but consumption appears to be rising on a worldwide scale. The factors contributing to this rise are complex but include such obvious reasons as the fact that improved medical care has resulted in wider coverage of the population. Recognition of new clinical syndromes may require further antibiotic use; there is also an increase in the number of new antibiotics available.

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[1] R. unpublished observations, 1977.

Much of the increasing use of antibacterial drugs is unnecessary (*5*). On many occasions they are employed without any clinical or laboratory examination. It is not suggested that laboratory support is always feasible or necessary, but there are many cases where rational therapy is possible only if culture data are available. Antibiotics are also used inappropriately in viral infections, in mild bacterial infections, which do not require such treatment, and in the many diarrhoeal diseases in which they are ineffective. In *Salmonella* gastroenteritis these drugs prolong the period of excretion (*6*). Authorities in some countries have already advised against the use of antibiotics in the treatment of salmonellosis except in special circumstances (*7*). There is often prophylactic application without a rational basis, as, for example, in mass chemoprophylaxis against cholera. Other factors, such as pressure exerted by patients and their relatives and promotion by the pharmaceutical industry, also contribute to the rapidly growing use of antibiotics.

5.2 Antibiotic use in animals

The uses of antibiotics in animals are as feed additives and for the prophylaxis or therapy of bacterial infections.

The use of antibiotics as feed additives for growth promotion is widespread. The commonest drugs currently used for this purpose are the tetracyclines—one of the most potent agents for provoking the emergence and selection of resistance plasmids and at the same time a very useful therapeutic agent. Antibiotics have been extensively but unsuccessfully used in animals for the prevention of infectious diarrhoea caused by salmonellae.

It is generally recognized that the use of antibiotics for animal salmonellosis may prolong excretion in animals as it does in man. *Salmonella* septicaemia is, however, accepted as an indication for antimicrobial treatment in animals as well as man, when chloramphenicol is the drug of choice if the strain proves susceptible in laboratory tests.

The rapid emergence and spread of drug-resistant salmonellae resulted from antibiotic use in animals during the 1960s (*8*). Transmission of these salmonellae to man resulted in many human infections, and the resistances of such strains, plasmidborne and chromosomal, were acquired in the animal host. Resistant enterobacteria colonizing man may not invariably have an animal source.

5.3 The role of food in the spread of antibiotic-resistant bacteria

This subject has been recently reviewed by a WHO Expert Committee on Microbiological Aspects of Food Hygiene (with the participation of FAO) (*9*) and by a Working Group convened by the WHO Regional Office for Europe.[1] The prevalence of drug-resistant enterobacteria in food has been demonstrated by many workers. The presence of antibiotic-resistant nonpathogenic enterobacteria in food is of public health significance. It is recognized that, although some food containing resistant bacteria is decontaminated during cooking, before being cooked it may contaminate other cooked or uncooked food in the kitchen and so transmit drug-resistant enterobacteria to man. Multiresistant nonpathogenic bacteria may add to the number of drug-resistant bacteria, with their plasmids, in the human intestine, but when the organisms concerned are pathogenic they may also produce foodborne diseases.

5.4 The role of sewage and surface waters

Sewage and surface waters contribute to the distribution and circulation of resistant organisms. They represent a natural medium in which R-plasmid transfer can occur under certain physical, chemical, or biological conditions. Sewage and surface waters contain resistant bacteria from human and animal wastes and can be regarded as a source of all plasmid types, which circulate and are selected under appropriate environmental conditions. These resistant bacteria from sewage and surface waters can be transferred under some circumstances to food and drinking-water, which leads to a recycling to man and animals (*10–12*).

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6. MEANS OF CONTROLLING THE SPREAD OF ANTIBIOTIC-RESISTANT BACTERIA

To ascertain whether a country has a problem of drug resistance, appropriate clinical specimens from nosocomial and enteric infections must be cultured regularly and the bacteria thus isolated tested for drug resistance on a continuing basis. Systematic collection and analysis of these data could provide an epidemiological basis for clinical and administrative guidance in the prevention and control of spread.

6.1 Rationale of surveillance

Information concerning the drug-resistance patterns of the prevailing pathogenic bacteria and the appearance of new resistance characteristics is of the utmost value for a proper selection of antimicrobial agents for therapeutic purposes. Unawareness of local drug-resistance patterns in pathogens may foster misuse and often overuse of antibiotics, with all their harmful consequences.

A national surveillance programme, in addition to ensuring early detection of the appearance of multiresistant strains, may guide clinicians in choosing the most suitable antimicrobial agent without laboratory examination of the particular isolate (for which facilities may in any case not be available), and may preclude the blind use of multiple antibiotics. It may also provide a scientific basis for the development of national and international policies concerning the manufacture, importation and use of antibiotics.

6.2 Health and economic benefits

Surveillance data, if properly used by health administrators and others responsible for the formulation of health policies governing the use of antibacterial drugs, could bestow both health and economic benefits. The economic benefits could follow from prevention of wastage and overuse of these agents. The costs of surveillance represent only a small fraction of the expenditure on improper use of antibiotics.

6.3 Surveillance and control of antibiotic-resistant bacteria in man

In the developed countries laboratory investigations are carried out to determine the organisms causing infections in man, and susceptibility tests are performed for clinical purposes as a guide to treatment. Such investigations are also undertaken in developing countries, although they are often limited to large cities. In many countries, such clinical data have also been used to provide epidemiological material for determining the incidence of resistant bacteria in human infections both in the hospital and in the community.

The main requirements for providing useful information in man are therefore to ensure: (*a*) that the medical microbiological services of a country are sufficiently well developed to study the problem of drug resistance; (*b*) that susceptibility tests are performed in a reliable manner to identify those antibiotics that need to be excluded because of drug resistance and those that might be clinically useful; and (*c*) that efficient means are available for collecting, processing and disseminating data as quickly as possible. The means for fulfilling these requirements are discussed in sections 8 and 9. Collection of information of this type should be given a high priority by health authorities.

Control of antibiotic use in man is very difficult, but every effort should be made to ensure the rational use of these drugs. This may be achieved by monitoring the emergence of antibiotic-resistant enterobacteria, formation of national antibiotic utilization committees, nationwide distribution of information concerning antibiotic-susceptibility patterns with profiles of antibiotic use, and establishment by WHO of an effective system for the wide dissemination of appropriate information on these topics.

The problems and control of antibiotic use in man can be dealt with only by educational methods. Steps should be taken to improve undergraduate and postgraduate education in the problem of drug resistance and the importance of rational chemotherapy of bacterial infection. Antibiotic substances should be made available only on prescription. The freedom of physicians to prescribe whatever antibiotics they may deem fit is difficult to limit, but some regulation of the use of a particular antibiotic in special circumstances may be required.

6.4 Surveillance and control of antibiotic-resistant bacteria in animals

The monitoring of enterobacterial resistance in domestic animals, which constitute a reservoir of resistance plasmids and a source of human infection, should be a function of veterinary and public health laboratories. The methodology of sampling and testing should be similar to that used in man.

There are several uses of antibiotics in food and in animals that require attention. The use of antibiotics as food preservatives should be discontinued, as other effective means of prevention of spoilage are available.

Therapeutic antibiotics cannot be used in the United Kingdom as feed additives (*1*) and the same is true for an increasing number of countries, such as Czechoslovakia, the Federal Republic of Germany and the Scandinavian countries. Restriction of the use of tetracyclines and penicillin in animal feeds appears to be imminent in the USA.

Animal growth promotion is achievable without the use of therapeutic antibiotics as feed additives.

The prophylactic use of antibiotics against infections in domestic animals should be critically reviewed. It should not be a substitute for high standards of animal husbandry. At present, it is not feasible to treat infections with different antibiotics from those used in man. However, such treatment must be on veterinary prescription. The educational needs of veterinarians in the appropriate use of antibiotics are similar to those of physicians.

6.5 Surveillance and control of antibiotic-resistant bacteria in the environment

The environment is continually being polluted by drug-resistant bacteria, but the public health importance of this contamination has not been fully ascertained. Investigation of the following factors, which will probably vary from place to place, may be important :

(1) Transmission of resistant bacteria by food likely to be eaten raw or undercooked.

(2) Presence of resistant bacteria in waste waters, sewage and animal wastes.

(3) Monitoring and disposal of refuse, particularly from hospitals, abattoirs and buildings used for livestock rearing.

(4) Influence of antibiotic use in plant diseases.

(5) Carriage of resistant bacteria by pets and wild life, including birds, insects and rodents.

Proper legislation to govern food handling and effective implementation of the regulations adopted are of basic importance.

6.6 Control of outbreaks of disease in man

Like all disease outbreaks, those caused by resistant bacteria should be brought under control, but they need energetic epidemiological investigation with a high standard of laboratory support to define the resistance pattern and distribution of the causative agent.

In the absence of trained epidemiologists, microbiologists with suitable experience serve well as epidemiologists. When an outbreak occurs, an appraisal must be made by grouping cases by date of onset, location and special features to enable the source to be traced. Case-control studies or cohort analysis may be necessary. As soon as the evidence of the source and vehicle is available, the relevant laboratory investigation should be instituted. Epidemiological findings should indicate the need for and determine the scope of laboratory investigations. The sampling procedures used will depend on the nature of the outbreak and the prevailing circumstances.

Community-acquired outbreaks of enterobacterial infection are usually foodborne or waterborne. If the responsible vehicle can be identified it must be withdrawn from circulation. If it is not possible to determine the vehicle of transmission, the public—especially in developing countries—should be urged to take hygienic measures (for example, boiling drinking-water and thoroughly cooking meat, shellfish, etc.). Facilities for treating ill persons should be available, as this encourages the reporting of cases, and prompt and effective treatment of cases also reduces transmission to other persons and to the environment. Restrictions on the movement of people and goods create hardships and economic losses, inhibit the reporting of cases and generate public alarm, thereby hampering efforts to deal rationally with the problem.

Although foodborne and waterborne illness may occur in hospitals, most resistant enterobacteria involved in nosocomial outbreaks are transmitted either by interpersonal contact or via contaminated fomites, although their relative importance varies by site and by pathogen. Control measures should be based on findings in epidemiological investigations. They include the enforcement of handwashing and the use of sterile techniques, the grouping of infected patients and carriers, appropriate isolation of infected patients, the elimination of contaminated fomites, and spatial dispersal of certain patients to minimize cross-infection. Antibiotic therapy is no substitute for recognized measures for the control of infectious diseases.

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7. LABORATORY METHODS FOR THE STUDY OF RESISTANCE IN ENTEROBACTERIA

7.1 Methods for determining the *in vitro* susceptibility of bacteria

Antibiotic resistance is usually tested with antibiotic-impregnated paper discs which allow diffusion of antibiotic into agar. This is a simple procedure if performed by a standard method. However, obtaining accurate, reliable and reproducible results from susceptibility tests is not simple, as several factors influence the results of testing. These factors can usually be controlled by performing the test simultaneously with reference strains.

Determination of the minimum inhibitory concentrations (MICs) of antibiotics for bacteria is performed on solid or liquid media containing graded concentrations of antibiotics. This gives a numerical answer which may be correlated with attainable blood or other body-fluid levels to assess whether infections with the organism are likely to respond to therapy.

Routine disc tests for antibiotic resistance are assessed by the diameter of the zone of inhibition, which varies with the diffusibility of the antibiotic and with the growth phase and rate of the organism (*1*). The problems inherent in this quick and simple method include variations in the composition of the media recommended for growing the organism, in the standardization of the inoculum, in the method of applying it to the plate, and in the content and stability of the antibiotic used in the disc. The presence of any of these problems should be detected when the control plates are read.

There are two aspects of susceptibility testing that require consideration : standardization of methods and quality control of the results.

Several attempts have been made to produce an internationally acceptable disc method for antibiotic susceptibility testing. These include the modified Kirby-Bauer technique (1975) (*2, 3*), which is widely used in the USA and elsewhere, the ICS[1] method (1971) (*4*) and the Stokes technique with internal standards (1972) (*5*). The objective of a standard method is to provide a defined technique that can be applied to almost all antibiotics and organisms, that will yield results indicating resistance or susceptibility in the majority of tests, and that is comparable with the methods used elsewhere.

It is unlikely that any one method will become the standard method of testing. It is therefore important to ensure that, whatever technique is employed, it has been fully evaluated and standardized before being used for reporting and that the technical details are carefully and precisely followed to avoid variations that will give rise to misleading results.

The main method for checking the correlation of agar diffusion test results with estimation of MICs is the construction of regression lines relating the MIC to the size of the inhibition zone produced by the antibiotic-containing disc. In drawing a regression line the zone diameters are plotted against the $\log_2$ MIC for each organism and a line is drawn to fit the points. The construction of these regression lines for each antibiotic to be tested is essential for the evaluation of each antibiotic/organism combination.

If the modified Kirby-Bauer method is performed according to directions (*6*), the interpretative tables given for that method for the rapidly growing Enterobacteriaceae may be used, and the contruction of regression lines is not required. However, if another established method is employed, then the regression lines specifically developed for that method must be used.

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[1] International Collaborative Study, sponsored by WHO and developed by the Karolinska Institute, Stockholm, Sweden.

Validation of the results of testing

There are several ways of validating the results. This is necessary to ensure that the *in vitro* results obtained are of value in prescribing suitable antibiotics for individual patients and also to permit the comparison of results obtained from different centres. Unless validation is carried out, results cannot be compared with any confidence. To ensure the reliability of the disc test all the following controls should be applied :

(1) *Reference culture used for internal quality control*

Reference strains are necessary to control the performance of the tests. With some methods a reference organism is included on the plate so that each test is controlled. Other methods require the use of a separate plate with reference strains for control. The number of such reference strains for control varies considerably between laboratories. The cultures that are usually used are susceptible strains[1] of *Escherichia coli* (ATCC 25922; NCTC 10418), *Staphylococcus aureus* (ATCC 25923; NCTC 6571) and *Pseudomonas aeruginosa* (ATCC 27853; NCTC 10662), which indicate deficiencies in the medium, inoculum and disc content. The appropriate control strain (or strains) should be used with each batch of routine daily tests. Sets of sequential values of zone diameter for these cultures are used for the evaluation of precision, accuracy and variability.

(2) *Control strains for resistance*

In order to test the performance of a method, some laboratories use a number of strains of *E. coli* with different antibiotic susceptibility patterns. These can also be used selectively in a control test on a batch of clinical isolates. The 12 strains listed in Annex 1[2] are satisfactory for checking the performance of methods devised for determining susceptibility in rapidly growing Enterobacteriaceae.

The twenty-eighth report of the WHO Expert Committee on Biological Standardization (*6*) gives details for the performance of the modified

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[1] These strains can be obtained from the American Type Culture Collection, 12301 Parkland Drive, Rockville, MD 20852, USA, or the National Collection of Type Cultures of Micro-organisms, Central Public Health Laboratory, Colindale Avenue, London, NW9, England.

[2] These strains, along with details of methods for preserving the plasmids, are available from the Department of Medical Microbiology, The London Hospital Medical College, London E1 2AD, England.

Kirby-Bauer technique. The recommendations for disc antibiotic content are based on those required for that technique.

In some countries where there is variation in the composition of the media and disc content, a method using controls on each plate—e.g., the Stokes method—may provide a more satisfactory procedure for clinical purposes than techniques which use a separate plate for examining the reference strains. Some technical details with regard to disc testing are summarized in Annex 1.

7.2 The nature and identification of resistance plasmids

A bacterium possesses a circular chromosome determining its genetic characters. The chromosome consists of DNA which is about 1000 µm in length and is regarded as constituting a single molecule.

Like the bacterial chromosome, resistance plasmids consist of circular DNA molecules the size of which is about 1–5% of that of the chromosomal DNA. Transferable resistance plasmids (R factors) consist of two different parts : one codes for drug resistance and the other for transfer. These parts may be linked so as to form a single molecule which transfers intact to the recipient bacterium. However, in some resistance-transfer systems, the molecule coding for resistance is independent in the host cell of that responsible for transfer. It is natural to postulate that in the second class of resistance factors, the molecule coding for resistance is associated with that coding for transfer while transfer is actually occurring.

Transfer in Gram-negative bacilli takes place by direct contact between donor and recipient cells—that is, by conjugation. This contact requires the presence of specific bacterial appendages known as pili or fimbriae, the synthesis of which is governed by the transfer factor.

The antibacterial drugs against which plasmid-mediated resistance has been detected in the enterobacteria are as follows : penicillin and related antibiotics ; chloramphenicol ; tetracyclines ; aminoglycosides ; and sulfonamides and trimethoprim.[1] Resistance to heavy metals such as mercury may also be plasmid-mediated. Other characters that may be determined by these agents are synthesis of enterotoxins, haemolysins and certain surface antigens, which may play an important part in bacterial pathogenicity and resistance.

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[1] Resistance to furazolidone, nalidixic acid and rifampicin is of chromosomal origin. Selection by the respective drugs of resistant mutants that carry resistance plasmids will also select for the plasmids concerned.

There are numerous different transfer plasmids in the enterobacteria. They can be classified according to their ability to coexist stably in the bacterial cell. It has been established that those that cannot coexist usually have a high degree of DNA homology, while those that can coexist do not show such homology.

In the resistance transfer systems in which the transfer plasmid is physically linked to the resistance determinant, the compatibility is that of the transfer plasmid. By contrast, when the resistance plasmid is separate from the transfer plasmid it has its own properties of compatibility with related plasmids which do not transfer themselves.

A single bacterial strain may carry several plasmids. Genetic and physical studies are important in the detection, isolation and identification of these plasmids, and in tracing the distribution and transmission of drug resistance in the enterobacteria. The relevant laboratory techniques are described in Annex 2.

Resistance plasmids have been encountered in all species of enterobacteria : *Escherichia coli*, *Salmonella*, *Shigella*, *Klebsiella*, *Enterobacter*, *Citrobacter*, *Serratia*, *Proteus*, *Providentia* and *Yersinia*. They have also been identified in *Pseudomonas*, *Aeromonas*, *Vibrio* and *Haemophilus*.

It is apparent that resistance transfer takes place *in vivo* in the intestine, but such transfer must also occur outside the human or animal host—probably in sewage or other highly contaminated surface waters.

The result of pressure by antibiotics is the selection of organisms carrying either complete resistance-transfer systems or resistance plasmids that can be mobilized by transfer plasmids. The maintenance of the selection pressure by antibacterial drugs expands the latitude of resistance and the density of the resistant bacterial population, which now forms an important part of the biosphere.

7.3 Sampling and examination of sewage and surface waters

The increasing frequency of antibiotic-resistant bacteria in surface waters may reflect ecological exchange between man and his environment. The bacteria involved are mostly enterobacteria and *Aeromonas* species. In urban waste waters, the concentrations of enterobacteria and *Aeromonas* are similar. The percentage of resistant bacteria varies greatly depending on a multiplicity of factors, from as little as 0.1% to as much as 100%.

Resistance to ampicillin seems to be most frequent, especially in *Aeromonas* species, which are also often streptomycin-resistant. Resistance to the tetracyclines is more frequent in faecal *E. coli* than in other enterobacteria. Many faecal strains of *E. coli* are chloramphenicol-resistant. In surface waters, the frequency of occurrence of resistant strains varies from 31% to 73% for at least one antibiotic, being highest for streptomycin. Over 80% of strains isolated from drinking-water after concentration are resistant to antibiotics. Multiple resistance is more frequently seen in strains from drinking-water, except in the case of *E. coli*, than in those from other types of water.[1]

Methods for sampling and testing the environment for resistant bacteria are described in Annex 3.

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8. COLLECTION AND PROCESSING OF DATA

As discussed earlier, it is necessary to utilize for epidemiological purposes data which have already been collected for clinical purposes. It is therefore important in setting up surveillance programmes to gather information in a form adaptable to epidemiological purposes without involving a great deal of time in the transcription of results. The data should thus be set out in a manner suitable for computer handling because a large volume of information will require processing. In peripheral hospitals transcription would presumably be manual.

The minimum of information required for surveillance of antibiotic-resistant enterobacteria is the following: patient identification, name of hospital or community source (whether urban or rural), relationship to any prevailing epidemic situation, date and source of isolation of the strain, name of reporting laboratory, and identification of the organism and its resistance pattern.

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[1] F. Mizon & H. Leclerc, unpublished observations, 1977.

The antibiotics that are often tested for clinical purposes include ampicillin, chloramphenicol, carbenicillin, the cephalosporins, gentamicin, kanamycin, neomycin, streptomycin, the sulfonamides, the tetracyclines and trimethoprim.

A centralized computer system, when available, is very useful for the analysis of raw data, and help should be sought from computer specialists to determine the type of programme that would be suitable for the available hardware and the health information system in use. Several systems of data analysis exist on a local, national or international level, and a pooling of expertise and facilities would permit much needed and accelerated advances in this field.

For the central collection and analysis of data to be successful and for a rapid response and offers of help to be forthcoming when epidemic situations arise, it will be necessary to ensure the rapid feedback of results to the participating institutions and to government agencies.

In multicentre studies of any type, problems of free exchange of information arise, particularly when infectious agents and antibiotic resistance are being dealt with. Disclosure of information may be impeded by a number of factors and the importance of exchange of information may not be sufficiently appreciated. If health workers are not fully aware of the significance of the information, specimens and data are collected in an irregular manner. This results in a marked variation in the amount and range of material received from different areas.

Communications between central reference laboratories and peripheral laboratories are often inadequate. The peripheral laboratories may on occasion be reluctant to refer strains and the relevant information to the central laboratory. Peripheral laboratories are often left in relative isolation with lack of feedback information, technical support, advice, quality control and proficiency testing. National reference laboratories have responsibilities in raising standards in peripheral laboratories and in ensuring continuous collaboration.

There is often no local mechanism for the exchange of laboratory information on current patterns of bacterial resistance to antibiotics in hospitals, communities, livestock and the environment. This information is required not only by the laboratories involved but also by practitioners and health administrators to ensure that appropriate action is taken.

9. ORGANIZATION OF A SURVEILLANCE PROGRAMME

9.1 Problems in surveillance of antibiotic resistance

There are several difficulties to be overcome before satisfactory surveillance programmes can be implemented. The problems which arise are common to all countries but have a different order of magnitude in developing countries.

There is often a lack of appreciation of the value of such information by practitioners and health authorities and consequently a lack of support for the activity in many countries. Only a small proportion of the total infections are monitored bacteriologically ; laboratory support is usually reserved for severe infections and treatment failures. In many instances laboratory facilities are either inaccessible or inadequate and the techniques are slow to deal with the clinical requirements. The lack of adequate facilities and of uniformity in techniques for susceptibility testing in different laboratories makes standardization difficult.

There is frequently a shortage of suitably qualified medical and technical staff to cope with the microbiological work. This shortage becomes more acute in countries trying to accelerate the development of their health services. In some countries efficiency may be improved by consolidating existing separate laboratory services for hospital, public health, university work, etc.

The establishment of an agreed simple system of surveillance may help to solve some of the obstacles outlined above. It could also bring about improvements in the general standards of laboratory work, make medical and veterinary personnel and administrators more aware of the problems, and improve communication not only between peripheral and central reference laboratories but also between veterinary and public health laboratories.

9.2 Use of information derived from a surveillance programme

The possible uses of information on resistant enterobacteria are as follows :

— to guide clinicians and veterinary workers on the appropriate use of antibiotics in their practices ;

— to form a basis for policies on the use of antibiotics in hospitals, in the community and in animal husbandry ;

— to provide information early on the drug-resistant pathogens in an outbreak of infection ;

— to indicate where special surveys are required in medical and veterinary fields ;

— to assist in revisions of hospital and national drug formularies ;

— to assist health administrators in decisions on the provision of antibiotics ;

— to ensure more reliable susceptibility testing for clinical purposes.

9.3 Requirements for the organization of surveillance of drug resistance

The prerequisites for organizing drug-resistance surveillance are listed below. The existing facilities and personnel should be used as far as possible.

(1) Appropriate government health officials must be convinced that worthwhile benefits will be derived and that the initial cost will not be great if existing laboratories and the professional and technical personnel can be persuaded that the programme of surveillance is feasible and important to the health of the country. However, in time, the programme, if it is to continue and be practicable, may require some additional funding. It is conceivable that this will be a small fraction of the amount derived from savings on antibiotic expenditure and disease treatment costs.

(2) The services of trained peripheral health workers, epidemiologists, public-health-oriented physicians and veterinarians, bacteriologists and technicians should be sought.

(3) A network of peripheral health and veterinary laboratories should be created.

(4) A central reference laboratory at national level (at regional level for several countries if they are small, or at area level if the country is big) would be required.

(5) A central epidemiological or disease intelligence unit to collect, interpret and disseminate the information should be set up.

Peripheral laboratories. The term " peripheral " is used in an administrative sense and is not intended to indicate that such laboratories are less efficient or have less capability than " central " or " national " laboratories. Peripheral laboratories may be hospital or university laboratories or local public health laboratories and should therefore have adequate facilities for basic bacteriological work. Many such laboratories will already be performing a number of the following necessary functions for the area in which they are situated : (*a*) ensuring the proper collection of specimens ; (*b*) isolating and identifying strains ; and (*c*) determining the drug-susceptibility pattern according to methods acceptable to the national reference laboratory. The results obtained should be sent to the clinicians and epidemiologists concerned, as well as to the national reference laboratory along with an agreed number of random strains when these are needed to validate the reporting.

National (central) reference laboratories. Ideally there should be a national reference laboratory for antibiotic resistance in each country. Failing this, a national laboratory for enteric bacteria could be expanded to cope with the responsibility if the capabilities exist. At national level it is desirable that human and veterinary reference laboratories should be closely associated.

The functions of a reference laboratory, whether at the national, regional or area level, should be :

- to develop standard methodology for sampling, for susceptibility testing and for preserving the strains and materials ;
- to collect, collate and interpret data from the peripheral laboratories and feed back to them information regarding technical performance ;
- to ensure that peripheral laboratories use proper techniques for identifying the strains, in collaboration with the national laboratory for enteric bacteria, and for susceptibility testing by quality control and by supplying appropriate reference strains and materials, etc. ;
- to provide training for bacteriologists and technicians in techniques, and for epidemiologists and peripheral health workers in the collection of specimens, etc. ;
- to evaluate the *in vitro* effectiveness of new antibiotics against the prevalent organisms in the country by well-controlled qualitative and quantitative tests ;
- when appropriate, to undertake genetic studies on the resistant strains to determine the mechanism of acquisition of resistance, or arrange for such studies to be undertaken with the assistance of WHO collaborating centres ;
- to maintain liaison with WHO collaborating centres for the exchange of information, the supply of reference strains and reagents, etc. ;

— to collaborate with the national epidemiology unit or disease intelligence centre in the training of health personnel, investigation of epidemics and dissemination of information to physicians and epidemiologists ;

— to provide information to the health authority for the development of appropriate policies concerning the importation, stockpiling and manufacture—as the case may be—of the country's supply of antibiotics ;

— to make recommendations to clinicians, veterinarians and public health authorities regarding appropriate action to be taken with regard to antibiotic use in man and animals.

WHO collaborating centres. The international or regional collaborating centres could provide valuable technical guidance and support at their respective levels to national laboratories. In addition, they might include training programmes, continuing education programmes, the administration of a quality control programme and the dissemination of periodic reports to interested individuals and institutions among their responsibilities.

10. SUMMARY

The Meeting was convened to review serious public health problems caused by infections with antibiotic-resistant enterobacteria and recommend methods for their surveillance and action to control their spread. Antibiotic resistance was defined and the mechanisms of resistance and the role of plasmids in the spread of resistance were reviewed.

Information on antibiotic resistance in the developing countries is in short supply and often there is no correlation of test results between countries. Most reports, however, show that antibiotic-resistant strains of enterobacteria, including *Salmonella*, *Shigella*, and *Escherichia coli*, are very common.

Several serious outbreaks of infection with resistant bacteria have occurred in recent years :

— antibiotic-resistant shigellosis in Central America, with many thousands of deaths, and in Bangladesh, with very high attack and case-fatality rates ;

— chloramphenicol-resistant typhoid fever in several parts of the world —for example, in Mexico in 1972, with many thousands of cases and a death rate similar to that of the pre-antibiotic era ;

- antibiotic-resistant salmonellosis associated with strains of animal origin ;
- resistant *Salmonella* infections in childrens' hospitals, with many deaths ;
- numerous hospital infections of many types caused by antibiotic-resistant strains of *Klebsiella*, *Serratia*, *Proteus*, *Pseudomonas* and *E. coli*.

In addition, resistance has now spread to involve other bacteria such as *Haemophilus influenzae* and *Neisseria gonorrhoeae*. There is a fear that further epidemics may result from this spread of resistance to other bacterial species.

The emergence of antibiotic-resistant bacteria is closely linked to antibiotic use in man, which is growing in all parts of the world. In some cases, the increase in antibiotic use is explicable because more people are receiving improved medical care. It is also associated, however, with the unnecessary administration of antibiotics in many cases. Control of antibiotic use in man is difficult but every effort should be made to ensure rational use—mainly by educational means.

The increase in antibiotic resistance is also connected with the use of these drugs in animals. The addition of antibiotics to feedstuffs as a means of growth promotion is still widespread, though this practice is declining as a result of the recognition of the role such feed additives play in the emergence of antibiotic resistance.

Many components of the environment—surface waters, waste waters, and sewage, for example—are becoming polluted with antibiotic-resistant bacteria, a development which requires careful monitoring.

Reliable laboratory methods for performing and reporting susceptibility tests need to be employed ; in this context the problems which arise in many countries over the supply of materials and equipment and the shortage of experienced personnel in microbiology laboratories must be borne in mind.

Other methods, which have a role in the elucidation of epidemiological problems, include those for determining the presence of resistance plasmids and for the study of drug-resistant enterobacteria in surface waters, waste waters, and sewage.

The training of personnel in adequate testing methods, in the use of antibiotics in treatment, and in the carrying out of epidemiological investigations is an essential part of the programme. The need is apparent for an effective system for data collection and analysis and for the dissemination of information, which would necessitate uniform reporting and the use of computers for data collection, processing and analysis.

Surveillance programmes for antibiotic-resistant enterobacteria should, as far as possible, use existing clinical and public health laboratory facilities. Such programmes would provide continuous assessment of the problems with antibiotic-resistant organisms and could give early warning of impending outbreaks of infection with the bacteria concerned. They would also furnish physicians with information enabling them to apply a more rational antibiotic therapy, and permit health authorities to make decisions on drug-related national policies, such as those concerned with the importation and production of antibiotics and their use in man and animals.

It is important to achieve close collaboration between epidemiologists, clinicians, veterinarians, health administrators and public health laboratories if surveillance programmes are to be effective. Surveillance would provide more appropriate antibiotic use and better health care. These benefits would more than offset the initial costs of establishing an effective system of surveillance.

11. RECOMMENDATIONS

(1) National programmes for surveillance should be established to monitor antibiotic resistance in enterobacteria.

(2) Monitoring of enterobacterial strains of animal origin and strains recovered from the environment should be included in a surveillance programme with the cooperation of veterinary and environmental scientists.

(3) Continuing education of medical practitioners, veterinarians and epidemiologists in the use of antibiotics in therapy and in feeds is required. Training programmes for laboratory workers, and a suitable training manual, are needed to ensure accurate and reproducible testing of antibiotic susceptibility.

(4) Laboratories should be encouraged to perform susceptibility testing of enteric bacteria by a reliable method that will generate comparable data (such as the susceptibility disc technique for which requirements have been established by WHO) and to submit their data for analysis. For this purpose, laboratories should report test results by zone diameter of inhibition, in addition to the notations " susceptible ", " resistant ", " intermediate " (or " reduced susceptibility " or " partial resistance ").

(5) Clinical, microbiological and epidemiological data collected at the local, national and regional levels should be compiled and analysed and made available to clinicians and health authorities for the formulation of national policies on the importation, manufacture and use of antibiotics.

(6) An information system for the collection of data from clinical and other sources should be established so that all the essential data are available on a form suitable for data processing.

(7) It is important to reach agreement on a computer system that would be the most appropriate for electronic data processing of information on antibiotic resistance ; for this purpose an international working group is considered essential.

(8) There is an urgent need to promote a programme of international surveillance of antibiotic-resistant enterobacteria and to establish international collaborating centres.

(9) Further research is needed on :

(*a*) simple methods for the standardization and evaluation of the means used to test bacteria for antibiotic resistance ;

(*b*) development of more rapid methods of susceptibility testing ;

(*c*) methods for the selection and preservation of reference strains for testing for antibiotic resistance ;

(*d*) methods of analysis of the results of susceptibility testing ;

(*e*) development of sampling methods to allow comparison of antibiotic resistance in hospital and community patients ;

(*f*) the clinical and epidemiological relevance of resistant bacteria in the environment ;

(*g*) development of effective methods for the control of resistant microorganisms of human and animal origin ;

(*h*) the factors influencing the emergence and disappearance of resistant bacterial strains and resistance plasmids ;

(*i*) the effect of susceptibility testing on physicians' attitudes and practices in prescribing antibiotics ;

(*j*) the effects of limiting or discontinuing the use of certain antibiotics in man or animals.

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Annex 1

NOTES ON THE PERFORMANCE OF DISC TESTING

Media for performance of the test

Bacteriological media vary considerably in their ability to support the growth of microorganisms. The size of the inhibition zone produced around a disc of antibiotic-impregnated blotting-paper will vary with the rate of growth of the bacteria being tested and the rate of diffusion of the antibiotic from the disc into the agar. Therefore, when deciding on the break-points of zone sizes between susceptible and resistant strains, it is necessary to correlate the zone size with the MIC of the antibiotic. To do this the zone sizes are measured and plotted graphically against the MIC. If an adequate number of strains are tested a regression line can be drawn for that antibiotic and the relationship of the zone size to sensitivity can be determined. Once a reliable relationship is drawn for a given drug/organism combination, that line can be used while that particular formulation of medium and a specified procedure are being used.

It is important to distinguish between agars for susceptibility testing and agars for antibiotic assay. The latter are not suitable for susceptibility testing because the constituents and pH vary in accordance with the requirements of the particular antibiotic assay for which they were designed.

Content of antibiotic on the disc

The content of antibiotic used on the disc has been defined for laboratories using an established method of testing, and the relevant information may be found in the bibliographical references in section 7.

If other techniques are being followed it should be noted that the correct disc content required to discriminate between susceptible and resistant strains will vary with the medium used and can only be determined by adequate testing in the user laboratories.

Inoculum size and method of inoculation

The size of the zone produced around a disc will vary with the inoculum size and the method used for inoculation of the plate. If a recommended method is not used it is important to employ a technique for obtaining an inoculum that gives a reproducible amount of growth resulting in a lawn evenly distributed over the plate. Most methods require a semiconfluent lawn but the Kirby-Bauer technique requires a confluent growth. Several methods of inoculation are used—e.g., flooding the plate or spreading the inoculum with a glass spreader or a swab. Flooding the plate is hazardous when highly pathogenic enteric organisms are being dealt with and is not recommended. Wire loops are unsuitable for adequate spreading of the inoculum but the other spreading methods are satisfactory provided that the optimum inoculum size is known. The optimum inoculum size varies with the method of application, but the correct inoculum can easily be obtained by suitable dilution of an overnight broth culture. However, routine susceptibility testing is usually performed on organisms isolated after primary cultures. For epidemiological purposes it is desirable that the susceptibility test should be performed on these isolates and not from the direct plating of specimens. To produce a semiconfluent growth the following method may be used. A wire loop is used to touch 5 colonies of the organism to be tested and the collected growth is emulsified in 3 ml of peptone water (or normal saline). A suitable growth is obtained by using a swab to spread a 3-mm loopful of the emulsion over the surface of the medium in a 9-cm Petri dish. The emulsion needs to be tenfold less concentrated if glass spreaders are used to inoculate the plate. The necessary judgement for preparing the amount of inoculum required to produce the correct amount of growth can only be acquired by experience.

In the modified Kirby-Bauer technique the inoculum suspension is judged with a barium sulfate standard to ensure a constant inoculum density.

Training in methods of susceptibility testing

In training programmes it is essential to aim for an understanding of the principles underlying the test and methods used to validate the results. Materials are likely to be of a different standard and no universal standard method can be applied. Therefore, workers performing the test will require good control methods to obtain reliable results.

The various methods of quality control were discussed earlier. The provision of reference strains of known sensitivity and resistance is one simple method of enabling peripheral laboratories to control their own tests. Annex Table 1 shows the MIC of 12 strains when these were tested by a technique employing the incorporation of graded concentrations of the antibiotics into solid agar and employing an inoculum of 10^4–10^6 organisms. Annex Table 2 shows the susceptibility of these strains when tested by a variety of disc methods on different media and represents consensus findings of several laboratories. Zone sizes are not given, as they will vary with the technique employed. It is possible that the reporting of zone sizes for these reference strains could provide some degree of validation of a disc test.

All the strains listed are nonpathogenic *Escherichia coli* and may contain plasmids. Like all plasmid-bearing strains, they are not completely stable and need to be kept lyophilized or on a defined agar containing antibiotic; in addition, they may have to be renewed periodically if the plasmids are lost. Other reference strains may need to be added as new antibiotics are introduced and resistances develop.

Annex Table 1

Minimum inhibitory concentration (MIC) (µg/ml) for reference (WL) strains

Antibiotic	Strain number											
WL	1	2	3	4	5	6	7	8	9	10	11	12
Ampicillin	1	128 +	1	128 +	128	32	128 +	2	128 +	128 +	32	128 +
Cefaloridine	2	16	2	4	128 +	4	32	2	8	128 +	4	32
Carbenicillin	2	128 +	4	128 +	2	128 +	128 +	4	128 +	128 +	128 +	128 +
Streptomycin	4	128	64	128	8	128 +	1	64	128	64	128	4
Kanamycin	2	0.5	2	1	4	4	64	1	128 +	V	32	32
Gentamicin	0.5	0.5	1	1	2	2	0.5	1	1	128 +	8	0.5
Sulfamethoxazole	4	4	128 +	16	4	128	2	128 +	128 +	128 +	128 +	16
Trimethoprim	0.25	0.5	1	1	1	0.5	0.25	1	32	128 +	128 +	0.5
Tetracycline	0.5	1	32	128	0.5	128	128 +	1	128 +	128 +	128 +	0.5
Chloramphenicol	2	2	128	1	4	128	2	128 +	128 +	128 +	8	2
Colistin	0.5	0.5	0.5	0.5	128 +	0.5	0.5	0.25	0.25	0.5	0.5	0.5

Note: V = Variable MIC and zone size.

Annex Table 2

Reference strains for the determination of antibiotic susceptibility

Antibiotic	Strain number											
	WL 1	2	3	4	5[a]	6	7	8	9	10	11	12
Ampicillin	S	R	S	R	R	R	R	S	R	R	R	R
Cefaloridine[b]	S	R	S	r	R	r	R	S	r	R	S	R
Carbenicillin	S	R	S	R	S	R	R	S	R	R	R	R
Streptomycin	S	R	R	R	S	R	S	R	R	R	R	S
Kanamycin	S	S	S	S	S	S	R	S	R	r	R	R
Gentamicin	S	S	S	S	S	S	S	S	S	R	R	S
Sulfonamide	S	S	R	S	S	R	S	R	R	R	R	S
Trimethoprim	S	S	S	S	S	S	S	S	R	R	R	S
Tetracycline	S	S	R	R	S	R	R	S	R	R	R	S
Chloramphenicol	S	S	R	S	r	R	S	R	R	R	R	S
Colistin	S	S	S	S	R	S	S	S	S	S	S	S

Note: S = susceptible; R = resistant; r = reduced susceptibility.

[a] This strain is a nonswarming *Proteus morgagni* included to check colistin.

[b] Strains producing β-lactamases that make them resistant to ampicillin also show reduction in zone-size diameter when tested against cefaloridine, which produced the pattern of reduced susceptibility.

Annex 2

LABORATORY METHODS FOR RESISTANCE (R)-FACTOR TRANSFER AND PLASMID ANALYSIS

Many of the techniques for the study of enterobacterial plasmids have been described by Anderson & Threlfall (*1*).

Tests for transferability of drug resistances

Broth cultures of donor and recipient strains are grown with shaking at 37 °C to exponential phase and contain approximately 2×10^8 organisms/ml.

(1) *Short crosses*. The cultures are mixed in a ratio of 1 : 10, usually 0.2 ml and 1.8 ml, and the mating is interrupted by the use of a high-speed blender. The duration of these crosses is usually 30 minutes, 1 hour or 2 hours.

(2) *Overnight crosses* (usually 18 hours). Donor and recipient cultures are mixed in equal volumes, usually 1 ml each, and incubated overnight. Crosses are performed at both 28 °C and 37 °C, because a few resistance plasmids are transferred with much higher frequency at 28 °C than at 37 °C. After each cross, decimal dilutions of the mixture are prepared in phosphate buffer, and either 0.01-ml or 0.1-ml quantities are plated in duplicate. The 0.01-ml quantities are streaked in linear fashion with a standard wire loop; 0.1-ml amounts are measured by pipette and plated with glass spreaders. Crosses are plated on minimal, MacConkey, nutrient or L agar, with and without suitable concentrations of the appropriate antibiotics. The plates are incubated overnight at 37 °C, and suitable plates are scored with a colony counter. The frequency of transfer in interrupted crosses is expressed as the proportion of resistant progeny per donor cell, while the transfer frequency in overnight crosses is calculated as the proportion per recipient cell.

Concentration of drugs in selective media

Drugs are used at the following concentrations to select for transfer of resistance:

benzylpenicillin	100 µg/ml
chloramphenicol	20 µg/ml

gentamicin	20 µg/ml
kanamycin	20 µg/ml
streptomycin	20 or 40 µg/ml
sulfathiazole	100 µg/ml
tetracyclines	5, 10 or 20 µg/ml

Counterselection against the donor strain

If the donor strain is sensitive to nalidixic acid, rifampicin or streptomycin, a strain chromosomally resistant to one of these agents is used as recipient. The drugs are used at the following concentrations for counterselection: nalidixic acid, 40 µg/ml; rifampicin, 100 µg/ml; streptomycin, 500 µg/ml.

In some experiments, colicin E2 is used to eliminate *Escherichia coli* K12 strains by spreading 0.3 ml of the colicin preparation on to each plate. Counterselection against *Salmonella typhimurium* strains is effected with the *Salmonella* 01 phage of Felix & Callow (*2*).

Most of these techniques for the detection of resistance transfer were described by Anderson & Lewis (*3*).

Mobilization of non-autotransferring plasmids

When there is no direct transfer of drug resistance, strains are examined for determinant mobilization in a triparental cross (*4*, *5*). Equal quantities (usually 1 ml) of a late exponential growth broth culture of the donor strain carrying a transfer factor, and of the intermediate strain with the non-autotransferring resistance, are incubated together for at least 2 hours. One millilitre of a broth culture of the plasmid-free final recipient is then added. The mixture is incubated overnight. The cross is plated on a medium which selects for the resistance carried by the intermediate strain, but counterselects against both donor and intermediate strains. A control mixture of the intermediate and final recipient is tested to establish that no transfer takes place in the absence of the transfer factor from the donor strain.

Plasmid-specific phage propagation experiments

Resistance plasmids are examined for their ability to stimulate their host strains to synthesize F- or I-type sex fimbriae. These are detected by testing for multiplication of the F-specific phages µ2 and fd or the I-specific phage If1 on the strains concerned (*6*). The strains are grown in nutrient broth to about 5×10^8 bacteria/ml, and 1 ml of each culture is diluted into 8-ml volumes of fresh broth. One millilitre of phage (titre 5×10^5 plaque-forming units/ml) is added to each diluted culture, so that the phage : bacterium ratio is about 1 : 1000. The mixture, and a control using a plasmid-free strain, are incubated overnight without shaking. After centrifugation, each supernatant is titrated in surface spot tests, using K12F$^+$ as indicator for phages μ2 and fd, and K12 carrying a derepressed mutant of the I-like R factor T-Δ as indicator for phage If1. The plates are incubated for at least 5 hours, after which the plaques are counted and the titre of phage is calculated for each test and control experiment.

Surface exclusion and compatibility tests

Exclusion of one resistance plasmid by another is measured by comparing the transfer frequency of one of the plasmids into an *E. coli* K12 plasmid-free recipient with the frequency into the same *E. coli* K12 strain carrying the second R factor. When exclusion is present, the frequency of transfer into the recipient carrying the second R factor is lower than that into the plasmid-free recipient.

Compatibility between two plasmids is determined by introducing one plasmid into a strain carrying the other, and examining recipient lines for persistence of this second plasmid. When both R factors are present in the progeny, segregation is monitored by growing the clones for 6 hours or longer in broth and plating suitable dilutions on nutrient agar. The following day, the master plates are replicated on to plates containing drugs corresponding to the resistances carried by each R factor. In general, three hybrid clones are plated and more than 100 colonies of each are replicated. Compatible R plasmids show a rate of segregation no higher than the rate of spontaneous loss of either parent factor. When the two plasmids are incompatible, however, less than 50% of the colonies usually retain both R factors. Compatibility experiments are generally performed on strains of *E. coli* K12. Plasmids are assigned to compatibility groups by their ability to coexist with R factors of known compatibility groups (*7*).

Tests for the fertility inhibition (fi) character

(1) *E. coli* K12 F$^+$ lines carrying the test plasmid are investigated for inhibition of visible lysis by the F-specific phage μ2. These tests are performed by spreading a loopful (0.01 ml) of a broth culture over an area of about 1.5-cm diameter on a nutrient agar plate. About 0.01 ml

of the phage is spotted in the centre of the inoculated area with a loop or pipette. The plates are incubated at 37 °C for about 5 hours (*8*).

(2) The resistance plasmids are transferred into *E. coli* K12 HfrH and recipient lines carrying the plasmid are tested for visible lysis by phage μ2, and for the frequency of transfer of chromosomal markers to *E. coli* K12 F^- in the 1-hour crosses. Cultures of donor and recipient strains in L broth are mixed in a ratio of 1 : 10, and recombinants are selected on minimal medium supplemented with appropriate amino acids, with 0.15% glycerol as the carbon source. Streptomycin (500 μg/ml) is used to counterselect against the *E. coli* K12 HfrH donor strain. Fertility inhibition caused by the plasmid in HfrH is detected by loss of visible lysis by F-specific phages, and by a reduction in frequency of transfer of chromosomal markers compared with that from the HfrH strain itself.

K12 F^+ and Hfr strains are both used in fertility inhibition tests, because certain plasmids displace the F factor from K12 F^+ lines (*9*). This displacement of F does not occur in Hfr strains where the chromosomal integration of the F factor gives it security of tenure.

Phage restriction by plasmids

Each resistance plasmid is transferred into the standard *E. coli* and *Salmonella* strains and the resistant progeny are tested for sensitivity to phages (*1*).

(1) *E. coli* K12 : Lines are examined for visible lysis by the " female-specific " phage φ2 (*10*) in surface spot tests.

(2) *S. typhimurium* phage type 36 : tested with routine typing phages (*11*).

(3) *S. paratyphi B* phage type 1 var. 2 : tested with routine typing phages (*2*).

(4) *S. typhi* phage type A : tested with routine typing phages (*12, 13*).

Investigations of plasmid DNA preparations

(1) Isolation of plasmid DNA and preparation of radioactively labelled plasmid DNA.

(2) Determination of plasmid molecular weights by electron microscopy.

(3) Analysis of plasmid DNA by agarose gel electrophoresis.

(4) Studies on the cleavage of plasmid DNA with restriction endonucleases.

(5) Radioactively labelled plasmid preparations are required for DNA-DNA reassociation experiments, in combination with total unlabelled DNA from plasmid-carrying strains, prepared by the method of Marmur (*14*).

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Annex 3

METHOD FOR SAMPLING AND TESTING THE ENVIRONMENT FOR RESISTANT ORGANISMS

Sampling

The detection and counting of antibiotic-resistant bacteria can be done in waste waters, surface waters (rivers, lakes, ponds and bathing places), and drinking-water. With waste water and surface water the untreated sample must be homogenized. Ultrasound treatment in a suitable apparatus has always proved satisfactory (30 seconds at 45 kHz).

After homogenization the samples are diluted serially tenfold down to 10^{-6} in 25% Ringer's solution and then seeded on suitable media.

With drinking-water, concentration of the microorganisms, theoretically few in number, is obtained by filtration of 100 ml through membranes. These are placed on Chapman's medium with triphenyl tetrazolium chloride (TTC) (*1*) and incubated at either 44 °C or 37 °C. Suspect colonies are then identified and an antibiotic susceptibility test is performed.

Bacterial species

The *Escherichia coli* group, including the faecal coli (FC), are sensitive and specific indicators of organic contamination, whether human or animal. They are indicators of faecal contamination, and the frequency with which they prove resistant to antibiotics will indicate how frequently they are resistant in the human flora. These bacteria are often abundant in the aquatic environment; they survive relatively well and theoretically do not multiply.

The " total coli " (TC) can refer to the FC and to other enterobacteria that are lactose$^+$ and ubiquitous. A parallel search can be made for these two groups of microorganisms by simple, rapid and relatively inexpensive techniques. The concentration of antibiotic-resistant FC in water will be an indicator of the utilization of antibiotics in hospitals, as additives in animal feeds, etc. The TC count will be more difficult to interpret in view of the heterogeneous origins of these microorganisms.

The *Aeromonas* group are aquatic bacteria. Their abundance and the frequency of resistant strains represent ecological changes.

Technical protocol

Organism counts are performed by spreading 0.1 ml of raw or diluted suspension on appropriate selective media :

— Lactose agar or bromocresol purple is suitable for counting FC.

— The reading of the dishes is done after 48 hours' incubation at 44 °C.

— Deoxycholate citrate lactose medium is used for studying TC after 48 hours' incubation at 30 °C.

— Von Graevenitz's medium contains deoxyribonucleic acid, toluidine blue and ampicillin, and can be used to demonstrate *Aeromonas*. Suspect colonies are counted after 72 hours' incubation at 25 °C.

For each sample of water, pure or diluted, and for the three types of microorganism under study, platings are made on solid media without antibiotics, which serve as controls (AT^-), and on media in which antibiotics have been incorporated (AT^+) at the following final concentrations : ampicillin (20 µg/ml), streptomycin (12.5 µg/ml), kanamycin (12.5 µg/ml), chloramphenicol (12.5 µg/ml) and tetracycline (12.5 µg/ml). The solutions of antibiotics are made in sterile distilled water and stored at 4 °C. Colonies may be picked from the plates for identification and for investigation by the susceptibility test performed with standard methods.

This procedure permits determination of the concentrations of FC, TC and *Aeromonas* present in the samples analysed, and calculation of the percentages of resistant bacteria for each antibiotic studied in relation to the total bacteria counts. Although precise and reproducible, this technique is relatively difficult to apply in routine practice, for it requires the seeding of 90 dishes of agar medium for the analysis of a single sample of water. However, it would seem to be the only practicable method. Any simplification in its application would compromise the information obtained.

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Society of Nematologists
Soil Science Society of America
Southern Weed Science Society
Weed Science Society of America
Western Society of Weed Science

May 28, 1980

The Honorable John D. Dingell
2221 Rayburn House Office Building
Washington, D.C. 20515

Dear Representative Dingell:

We understand that you have recently introduced HR 7285 to amend the Federal Food, Drug, and Cosmetic Act to limit the antibiotic drugs which may be used in subtherapeutic doses in animal feed. The purpose of this letter is to call your attention to a report on antibiotics in animal feeds in preparation by the Council for Agricultural Science and Technology. We shall send you a copy as soon as the report is completed.

Sincerely,

Charles A. Black

Charles A. Black
Executive Vice President

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Headquarters: 250 Memorial Union, Ames, Iowa 50011 Telephone 515-294-2036 or 2803

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Weed Science Society of America
Western Society of Weed Science

June 1, 1980

Mr. Richard Fortuna
c/o The Honorable John D. Dingell
2221 Rayburn House Office Building
Washington, D.C. 20515

Dear Mr. Fortuna:

CAST President Ralph W. Fogleman was out of town on Friday, and so I was unable to contact him. I caught him on Saturday and have discussed with both him and the antibiotics task force chairman Virgil W. Hays your request for a draft copy of the CAST report on antibiotics in animal feeds.

We appreciate your interest in the report and understand your need to have all the information available in connection with Congressman Dingell's bill. As I explained on the telephone, the economic section of the report is the part that is holding us up, but we would be subject to censure even if we were to send you the other parts marked "Draft, Not For Publication." I am enclosing a copy of our "Policies and Guidelines" that will show the code by which we operate.

We should have the report done in a couple of months, and we shall send you a copy as soon as it is available. We hope it will reach you before final action is taken on the bill.

As a possible help to you in the meantime, I am enclosing a list of task force members. If you hold hearings on the bill, you may want to contact some of these persons for testimony. I suggest that you start with the chairman. He can advise you on the areas of expertise of the other persons on the task force.

Sincerely,

Charles A. Black

Charles A. Black
Executive Vice President

cc: Task Force Members
Ralph W. Fogleman

TASK FORCE MEMBERS

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Western Society of Weed Science

June 27, 1980

The Honorable John D. Dingell
United States House of Representatives
Washington, D.C. 20515

Dear Representative Dingell:

I am writing with regard to your recent testimony on HR 7285 "To amend the Federal Food, Drug, and Cosmetic Act to limit the antibiotic drugs which may be used in subtherapeutic doses in animal feed." According to information received in this office, you testified in part as follows: "I note with some curiosity the NAS exceedingly cautious tones and their inclusion of a yet to be released report by the Council for Agricultural Science and Technology. In light of the resignations of seven distinguished scientists en masse from the CAST panel on antibiotics in feeds due to coercive and deceptive attempts to bend science in a manner favorable to the pecuniary interests of the CAST membership, I question the National Academy's use of the CAST paper as a resource for its report."

We chose not to respond in kind to the allegations made by the scientists who resigned from the CAST antibiotics task force to the accompaniment of various statements to representatives of the media. Instead, we made a number of attempts to persuade the persons concerned to complete the work they had agreed to do when they became members of the task force. Regretfully, we failed.

The scientists who resigned, however, had ample opportunity to present their subject matter in the way they wanted to present it, including preparation of a separate report with an editor of their own choosing who would be paid by CAST. This would hardly classify as "coercive and deceptive attempts to bend science in a manner favorable to the pecuniary interests of the CAST membership."

The CAST Executive Committee has made a careful review of the circumstances leading to the resignation of the scientists from the task force on antibiotics in animal feeds and has concluded that the conditions of participation of these scientists were not responsible for their withdrawal from the task force activity at the first-draft stage. A copy of the report prepared by the Executive Committee is enclosed for your information.

Sincerely,

Ralph W. Fogleman

Ralph W. Fogleman
President

THE PUBLIC HEALTH RESEARCH INSTITUTE
OF THE CITY OF NEW YORK, INC.
455 FIRST AVENUE, NEW YORK, N. Y. 10016
TEL. (212) 481- 0746

July 3, 1980

The Honorable John Dingell
The House of Representatives
Washington, D.C. 20515

Dear Mr. Dingell:

Enclosed is a letter detailing the events around the resignation of six scientists from the CAST task force on antibiotics in animal feeds. Enclosed also is a copy of an article from Biosciences magazine about CAST and a letter I had written in response to the article. This letter gives certain additional details of the activities of CAST in connection with their antibiotics in feeds task force.

I would like, incidentally, to commend you on your eloquent testimony and for your courageous action with Mr. Waxman in introducing the antibiotic Preservation Act, HR7285, which is a major step in the necessary legislative remedy for the ubiquitous overuse of antibiotics.

Sincerely yours,

Richard Novick

RN/lk

THE PUBLIC HEALTH RESEARCH INSTITUTE
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July 3, 1980

The Honorable John Dingell
The House of Representatives
Washington, D.C. 20515

Dear Mr. Dingell:

In connection with a letter written to you by Ralph Fogleman President of CAST, dealing in part, with our collective resignation from the CAST Task Force on Antibiotics in Animal Feed (AFTF), we should like to affirm that your testimony to the effect that we resigned "due to coercive and deceptive attempts to bend science in a manner favorable to the pecuniary interests of the CAST membership" is a reasonable (though somewhat simplified) characterization of the reasons for our resignation. We enclose several of the relevant documents outlining our position; these should provide the appropriate background information and should confirm the essence of your view. We would point out, however, that the pecuniary interests involved are more directly those of the organizations that support CAST than those of the members themselves, many of whom are academicians.

The documents enclosed are:

1) A copy of our letter of resignation from the AFTF dated December 13, 1978. In summary, this letter stated that an interim summary of the AFTF deliberations was prepared and published prematurely under pressure from CAST headquarters and without adequate discussion. In particular, our views were toned down and effectively buried under a highly favorable economic analysis that had never been discussed or reviewed by the Task Force. It also stated that CAST had invalidated the work of the AFTF by taking an official and public position in defense of the use of antibiotics in feeds in response to a TV show critical of this position while the deliberations of the AFTF were still in progress. Further, this CAST position paper had been prepared by a second, smaller task force consisting of four of the members of the AFTF and chaired by Virgil Hays, the Chairman of the AFTF. Our letter concluded with the statement that the final AFTF report would contain voluminous material on the economic benefits of antibiotics as feed additives that were neither adequately documented nor subjected to critical review by the overall group.

It was concluded that CAST was a prior advocate of a definite position and would therefore be inherently unable to prepare an unbiased analysis, and had not acted in good faith throughout the entire procedure in respect to these matters.

2. We enclose also a copy of a memo to Charles Black, dated February 21, 1979, from the members who resigned, in response to his request that we reconsider.

3. We enclose also copies of correspondence between Dr. Black and Dr. Julian Davies that delineates the deceptive methods used by CAST. This correspondence relates to an unidentified delegation of CAST board members sent by Dr. Black to Dr. Davies, who had resigned from the AFTF, to attempt surreptitiously to re-recruit him to complete the part of the AFTF report that was our responsibility.

These materials speak for themselves and, I think, fully counter the position expressed in Fogleman's letter and support your own.

Sincerely yours,

Richard P. Novick, M.D.
Chief, Department of Plasmid Biology
Editor-in-Chief, PLASMID

Signature authorized by telephone:

Roy Curtiss III
Professor of Microbiology, University of Alabama, Birmingham

Julian E. Davies
Professor of Biochemistry, University of Wisconsin

Vickers Burdett (Hershfield)
Assistant Professor of Microbiology, Duke University

Michael Haas, Ph.D.
Department of Medicine, University of Wisconsin

Raul Goldschmidt
Visiting Professor of Microbiology, University of Alabama, Birmingham

December 13, 1978

MEMORANDUM

TO: Virgil W. Hays

FROM: Roy Curtiss III, Julian Davies, Raul Goldschmidt, Michael J. Haas, Vickers Hershfield and Richard Novick

SUBJECT: CAST Task Force on Antibiotics in Animal Feeds

On November 17 and 18, 1977, the CAST Task Force on Antibiotics in Animal Feeds met in Lexington, Kentucky to review, discuss and suggest modifications in the draft reports submitted by individual Task Force members in an attempt to reach consensus conclusions based on evaluation of the published literature pertaining to the use of antibiotics in animal feeds. As you are well aware, many sections of the report required substantial rewriting and certain important sections which had not been written at the time of the meeting were to be drafted later and then discussed by members of the Task Force. An interim summary that could be used by CAST to submit to FDA relative to FDA's proposed regulations on the use of penicillin as an animal feed supplement was prepared at the end of the second day of this meeting even though the Task Force had not yet completed discussion of those individual draft reports that were available for review. This interim summary document was hastily drafted by three members of the Task Force and was then presented orally to the entire group for comment and approval. You, as Chairman of the Task Force, wrote down agreed-upon revisions, although time constraints and the confusion associated with revision of a document that was not available in written form for Task Force members left it unclear what suggested modifications were, in fact, to be incorporated in the final interim summary document. You also took responsibility for typing and editorial revision of this document following adjournment of the Task Force meeting. CAST submitted this interim summary to FDA without further revision and with no opportunity for review and comment by members of the Task Force. In reading the interim summary document that had been sent to FDA, we noticed that some of the experimentally validated conclusions pertaining to the human health aspects of antibiotic usage in animal feeds had been weakened or dulled. These realizations were particularly bothersome to us since our primary responsibility as members of the human health subcommittee of the Task Force was concerned with the effect of antibiotic usage in animal feeds on human health. Furthermore, in view of the factual evidence presented in the reports of the different Task Force subcommittees, the absence of certain reports such as that on economic impact of antibiotic usage in animal feed, and the discussions at the meeting of the Task Force, the interim summary document submitted by CAST to FDA seemed to us tendentious in its systematic use of qualified statements concerning the human health aspects while at the same time using much more categorical language in dealing with the section on economic impacts. Some of us indicated to you our serious concern and disturbance about the changes introduced into the section of the interim summary dealing with human health aspects and furthermore noted the discrepancies between the conclusions of the reports presented to and discussed by the Task Force and the statements made in the interim summary sent to FDA. The text of this interim summary report was, therefore, the first indication that the conclusions derived from the documented evidence collected by each of us and submitted in written form to other members of the Task Force would be ignored or at least distorted in statements issued by CAST to governmental regulatory agencies.

We recently learned that CAST created another Task Force which had a function that paralleled that of the CAST Task Force on Antibiotics in Animal Feeds since it was charged with evaluating the content of an ABC - T.V. documentary that dealt with the use of antibiotics in animal feed (News from CAST 1978, Vol. 5:33-34 and Vol. 5:40-41). This Task Force was composed of four members, all of whom are also members of the Task Force on Antibiotics in Animal Feeds and you were its Chairman. Since the CAST Report No.76 entitled "Antibiotics in the Barnyard" and the News release issued by CAST were largely concerned with the subject of bacterial drug resistance, we consider it indeed strange that none of us was asked for his or her opinion on this matter since our reports to the CAST Task Force on Antibiotics in Animal Feeds dealt extensively with this subject which is in our collective sphere of expertise, whereas none of the four members of this special Task Force can claim either appropriate training or sufficient knowledge to evaluate objectively the experimental findings in that area. It is clear to us that the news release and CAST Report No. 76 contain several factual errors and omissions concerning bacterial drug resistance and its influence on human health and therefore state some conclusions and suggest still others which are invalid.

The circumstances described in the preceding paragraphs create a paradoxical situation for us and place us in a professional dilemma. First, we do not understand why CAST sought our expertise on the CAST Task Force on Antibiotics in Animal Feeds and then in writing statements for FDA and in criticizing the ABC - T.V. documentary either disregarded or misrepresented the information and conclusions contained in our reports to CAST on bacterial drug resistance and its effect on human health. Second, the fact that CAST established a special Task Force to deal with the issue of antibiotics in animal feeds and whose report included some statements in our field of expertise that are inaccurate and misrepresent the available scientific data creates a special and serious professional problem for us since our participation in the CAST Task Force on Antibiotics in Animal Feeds is known to many and our names are easily associated with statements drafted by this other Task Force appointed by CAST.

Whatever motives CAST might have had in asking us to serve on the Task Force on Antibiotics in Animal Feeds, we must conclude that our considerable efforts in collecting data and drafting reports for inclusion in the final report of the Task Force, as well as our participation in meetings of the Task Force to discuss all of the relevant issues, have been construed by CAST to be only of peripheral importance and a contribution and effort that need not be honestly considered by CAST in putting forth statements on the hazards and benefits associated with the continued use of antibiotics in animal feeds. This is clearly evident from a review of the Draft Final Report of the CAST Task Force on Antibiotics in Animal Feeds sent from your office on September 21, 1978 and the edited version of this report distributed by Dr. Charles A. Black, Executive Vice President of CAST, on December 4, 1978. We note that certain sections drafted by us and presented to and discussed by the Task Force last November and which contain information that we believe is pertinent to the issues in question have been deleted. Furthermore, statements and conclusions in the remaining sections on antibiotic resistance in bacteria and human health that are substantiated by published data have been editorily revised and/or omitted. We also note that other sections never presented to nor discussed by the Task Force have been inserted in the Draft Final Report and these sections contain statements and conclusions that are often unsubstantiated. Thus the Final Draft Report contains numerous inaccuracies and is misleading. It is evident, therefore, that neither does the Draft Final Report represent a consensus of the Task Force members nor can we envision the possibility of reading such a consensus under the particular circumstances created by CAST.

Therefore, after long and thoughtful deliberation, we deem it necessary to resign collectively from the CAST Task Force on Antibiotics in Animal Feeds. This resignation carries with it an explicit prohibition of the publication or other use by CAST in connection with the report of the Task Force on Antibiotics in Animal Feeds or with any other activities of CAST of any of the written materials that any of us has contributed to the Task Force during the past two years. We instruct you, therefore, to remove in their entirety our several remaining contributions comprising pages 15 through 90h inclusive of the Draft Final Report of the CAST Task Force on Antibiotics in Animal Feeds as was distributed to all Task Force members on September 21, 1978 and return to us these materials as well as all our original contributions sent to you in 1977. We also instruct you to eliminate our names from the final Report of the Task Force and publicly from the "Interim Summary" of the Task Force which was issued on November 23, 1977 without our collective approval.

We regret the necessity of taking this action; we are doing so despite the time and effort that we have thus far expended because CAST has not acted in good faith with respect to its announced intention to prepare an unbiased report on antibiotics in animal feeds and has taken a public stand before the publication of the final report that is both a direct contravention of neutrality and a misrepresentation of our contributions as members of the Task Force.

Roy Curtiss III

Julian Davies
Julian Davies

Raul Goldschmidt

Michael J. Haas
Michael J. Haas

Vickers Hershfield
Vickers Hershfield

Richard Novick

cc: Members of CAST Task Force on Antibiotics in Animal Feeds
Dr. Charles A. Black
Dr. Donald F. Kennedy
Members of Senate Committee on Agriculture, Nutrition and Forestry
Members of House Committee on Agriculture

February 21, 1979

MEMORANDUM

TO: Charles A. Black

FROM: Marvin P. Bryant, Roy Curtiss III, Julian Davies, Raúl Goldschmidt, Michael J. Haas, Vickers Hershfield and Richard Novick

SUBJECT: Your Memorandum of January 22, 1979 regarding CAST Task Force on Antibiotics in Animal Feeds

We have devoted considerable time discussing your memorandum that was written in response to our resignation from the CAST Task Force on Antibiotics in Animal Feeds. Although we fully share your views on the stimulating role of controversy in the advancement of science and concur with the goals and charges you established for the CAST Task Force at the time of its formation, we were disappointed that you made no serious attempt to answer our criticisms of CAST's behavior which were the basis for our resignation from the Task Force. Furthermore, it is evident that our perception of CAST's efforts to facilitate the preparation of an accurate, objective and complete report on the use of antibiotics in animal feeds differs significantly from yours.

In the spring of 1977, we agreed for several reasons to serve as members of the CAST Task Force on Antibiotics in Animal Feeds. First, we subscribed to the goals for the Task Force as stated in your letter of May 19, 1977 to write an accurate, objective and complete report that would not contain recommendations or promote or oppose policies except on the basis of scientific validity. Second, we believed that we could make valid contributions to this effort because of our collective expertise on mechanisms of antibiotic resistance, microbial and molecular genetics and microbiology. Third, we believed that our evaluation of the relevant scientific literature would be unbiased since we had never conducted research directly pertinent to the issue of antibiotic usage in either agriculture or medicine and thus would not have to evaluate our own research contributions. Furthermore, we had never received either research support or consultantships that would compromise our objectivity in considering the consequences of antibiotic usage in agriculture.

Although we attach different levels of significance to some research reports within our realm of collective expertise than do other members of the CAST Task Force, the basis for our displeasure and disagreement with CAST has little or nothing to do with such purely scientific issues. Apparently you misconstrued what we stated in our December 13, 1978 memorandum to Dr. Virgil W. Hays, chairman of the CAST Task Force on Antibiotics in Animal Feeds. It will thus be useful to briefly reiterate our remarks and then offer additional comments to remove any ambiguity which may exist.

In our memorandum, we noted that in both the interim summary written in November, 1977 and sent to FDA and in the two Draft Final Reports of the Task Force distributed on September 21 and December 4, 1978, some of the experimentally validated conclusions pertaining to the human health aspects of antibiotic usage in animal feeds had either been amended with selectively weakening qualifications or omitted.

In addition, we expressed our serious concern with the creation by CAST of a four-member Task Force which had a function that paralleled that of the CAST Task Force on Antibiotics in Animal Feeds. This new Task Force, whose chairman and members were also chairman and members of the Task Force on Antibiotics in Animal Feeds, was charged with evaluating the content of an ABC-TV documentary that dealt with the use of antibiotics in animal feeds. The report and news release written by this other Task Force dealt extensively with the subject of bacterial drug resistance in spite of the fact that none of its four members was either trained or had sufficient knowledge and expertise in that area. Based on the above considerations, we therefore concluded that CAST had not acted in good faith with regard to its stated intention to prepare an unbiased report on antibiotics in animal feeds and had, in addition, taken a public stand before the publication of the Final Report that was a direct contravention of neutrality and a misrepresentation of our contributions as members of the Task Force on Antibiotics in Animal Feeds.

While you state in your January 22 memorandum that we were invited to participate as members of the Task Force on Antibiotics in Animal Feeds because, in your considered opinion, science and society are best served by a report from CAST that carries the whole story, our experience reveals several contradictions to this assertion. For example, as members of the Task Force subcommittee on human health, it was immediately apparent to us that the chapter of the Draft Final Report entitled "Antibiotics in Human Health" contained significant omissions:

1. It was agreed at a Task Force meeting that a section of the human health chapter needed to be written that would document any changes during the past 30 to 40 years in the species of bacteria causing human infectious diseases as well as the changes in antibiotic sensitivity and resistance of these bacterial infectious disease agents. Unfortunately, the Task Force member most expert on human bacterial infectious diseases did not write this report; we repeatedly noted this omission to Dr. Hays with the suggestion that another infectious disease expert be appointed to remedy this situation. This information is still missing from the report.

2. We previously suggested that information for the conclusion reached some years ago that subtherapeutic levels of antibiotics were ineffective for disease control in humans and the basis for the decision to ban use of such nonprescription antibiotics by humans in the U.S. be included in the Task Force report. We also suggested that information on the basis for and the impact of regulations promulgated by many European countries that restrict use of subtherapeutic levels of antibiotics in animal feeds be included. We note in your memorandum of January 22, 1979 that CAST is now interested in securing the latter but not the former information.

3. In reviewing the section on antibiotic residues in meat and animal wastes, we noted at the November, 1977 Task Force meeting and later in conversations with the author that certain information was missing. The report dealt almost exclusively with tetracycline, while we believe that information on all the antibiotics approved by FDA for use in animal feeds should be evaluated. Furthermore, since the report indicated that tetracycline was concentrated in the kidneys, it was evident that data on excretion of tetracycline in urine was needed as well as the information provided on excretion in feces. As chairman of the Task Force, Dr. Hays was aware of these omissions and could have arranged for completion of this segment of the human health chapter.

In further contradiction with your laudable statement about telling the whole story, we experienced difficulty and delays in trying to obtain data from studies conducted by the chairman of the Task Force and by investigators at American Cyanamid, a company that we later learned was a supporting member of CAST. This unexpected lack of cooperation in supplying information was in distinct contrast to the helpfulness of other scientists and also of staff members at FDA and CDC.

When we initially joined the Task Force we knew little about the complexity of the issues concerning antibiotic addition to animal feeds and the voluminous information on this subject that had to be evaluated. In hindsight, however, it is difficult for us to understand how CAST, aware of these facts, could state the intention of preparing a report that would carry the whole story, yet at the same time expect the Task Force to evaluate all pertinent information and to write a complete report concurred upon by all Task Force members in a single two-day meeting.

An additional issue of concern to us is the lack of uniformity among the different sections of the Draft Final Report in adhering to your charge to the Task Force to be objective and accurate and refrain from making recommendations. The two chapters dealing with "Antibiotics and Human Health" and "Animal-Health and Animal-Production Aspects of Antibiotic Usage" deal with the published scientific literature and by and large only contain conclusions and inferences that derive from review of the published research data. On the contrary, the chapters on "Socio-Economic Implications of Antibiotic Usage in Livestock Production", "Economic Benefits of Antibiotic Usage in Livestock Production" and "Legal Status of FDA Proposed Restrictions" are not based on research data. The chapter on legal issues states "conclusions" on what FDA should do and how they must do it and clearly represents the legal opinion of the author which cannot be evaluated by other Task Force members. It therefore does not belong in the report at all. The chapters on social and economic impacts, on the other hand, could contain useful analyses and predictions based on valid assumptions stemming from the published data on the influence of antibiotic usage on human health, animal health and animal productivity. Unfortunately this has not been done. The chapter on "Economic Benefits of Antibiotic Usage in Livestock Production" is sufficiently incomplete and misleading to be easily criticized by non-economists. The title states an unsubstantiated conclusion and the word "benefits" should be replaced with the word "impacts". All the studies cited assume that (i) the growth promotion achieved by feeding subtherapeutic levels of antibiotics as determined by experiments conducted in the 1950s and 1960s will remain unaffected despite the gradual increase in antibiotic resistance of animal pathogens as has been noted in various studies conducted in the 1970s and (ii) that all antibiotic feed additives would be banned. The first assumption may or may not be valid but should be explicitly stated. The second assumption is invalid and its use is misleading. The FDA has only proposed restrictions on using tetracycline and penicillin in animal feeds and thus one must consider the difference in benefits in continuing to use tetracycline or penicillin vs. substituting other antibiotics approved by FDA for use as animal feed additives. Also, since the economic benefit predictions are based almost solely on data on the growth promotion effects of antibiotic usage, it would seem equally valid and important for an overall objective treatment to also make predictions of economic impact based on the effects restricting use of penicillin and tetracycline in animal feeds might have on human and animal health.

The foregoing comments reflect the basis for our displeasure and disagreement with CAST. They also substantiate our belief that CAST is not committed to the preparation of an objective, accurate and complete report on the consequences of adding antibiotics to animal feeds.

In spite of the foregoing, we have given careful consideration to the four alternatives that you proposed in your January 22nd memorandum for our reappointment to the Task Force. Actually, it has been the discussion generated by consideration of these as well as other alternatives that has contributed to the delay in responding to your memorandum.

None of your proposals as stated is satisfactory. Your first alternative, however, if appropriately modified with assurance for honest implementation, would have represented the most desirable course of action. This is because we believe that it would be possible to write an objective, accurate and complete report on the effects of using antibiotics in animal feeds and to achieve consensus on its contents. This, however, could not be achieved by limiting the number of additional meetings of the Task Force. You must realize by now that your original contention, stated in your letter of May 19, 1977, that the Task Force could draft a consensus report in one two-day meeting in June of 1977 without access to the published literature and with no time to evaluate the available data was most naive and, in terms of your charges to the Task Force to write an accurate, objective and complete report, a scientific absurdity. The information that would need to be evaluated, some of which is not published, is voluminous and is written in many different languages. Obviously, all members of the Task Force would need to do more homework and individuals with new expertise and with no conflicts of interest would have to be added as new Task Force members. Several meetings would thus be needed to realize the benefits of open scientific discussion and debate so as to achieve consensus in drafting a final report. Furthermore, assurance of editorial control over the summary statement and final report would have to be vested with Task Force members.

Based on our past experience with CAST as documented above and in our December 13, 1978 memorandum to Virgil W. Hays, we are of the opinion that CAST does not have the inclination, capability or resources to write an objective, honest and accurate report dealing with all aspects of antibiotic usage in animal feeds; had this been your desire at this late date, we would have anticipated that you would have realized the need for adding the refinements described above to your alternatives proposed to us. Moreover, now that we have analyzed much of the research literature that is relevant in evaluating the consequences of adding antibiotics to animal feeds, we wonder whether another report on the subject would be particularly useful; after all, a number of good reports have been written and many European countries have already evaluated the existing literature and decided to restrict use of some antibiotics in animal feeds.

Your memorandum of January 22nd contains additional statements that are deserving of comment. First, you state that none of us communicated any suggested revisions to the Draft Final Report of the Task Force to Dr. Hays after he sent it to Task Force members on September 21, 1978. That is true, but in reading the draft we noted that our previously communicated suggestions for preparation of an accurate and objective report that would deal with all aspects of antibiotic usage in animal feeds had been ignored with the exception that some of our suggestions for revision of the section on animal health had been considered. We also realized that some of our contributions which were in conflict with what we began to perceive as CAST's preestablished positions had been deleted. We thus experienced general dissatisfaction and frustration and deemed that reiterating these suggested revisions which are cited above along with enumerating the many minor and major errors would be futile in view of our other experiences as members of the Task Force.

Second, your statement about the public source of our salaries mandating a responsibility to work together in the public interest, with the implication that by resigning from the Task Force we were being irresponsible and acting in conflict with the public good, is a bit arrogant. We believe our action to resign from the Task Force with a full disclosure of the basis for our resignation to have been the only responsible course of action and in concert with the public interest.

In closing, we reiterate the instructions stated in our December 13, 1978 memorandum to Dr. Virgil Hays concerning use of the reports written by us. Since we are no longer members of the Task Force on Antibiotics in Animal Feeds, we again inform you that our resignation from the Task Force carries with it an explicit prohibition of the publication or other use by CAST in connection with the report of the Task Force on Antibiotics in Animal Feeds or with any other activities of CAST of any of the written materials that any of us has contributed to the Task Force during the past two years. We instruct you, therefore, to remove in their entirety our several remaining contributions composing pages 15 through 90h inclusive of the Draft Final Report of the CAST Task Force on Antibiotics in Animal Feeds as was distributed to all Task Force members on September 21, 1978 and again on December 4, 1978 and return to us these materials as well as all our original contributions sent to Dr. Virgil W. Hays in 1977.

cc: Dr. Virgil W. Hays
Members of the CAST Task Force on Antibiotics in Animal Feeds
Dr. Donald F. Kennedy
Members of Senate Committee on Agriculture, Nutrition and Forestry
Members of House Committee on Agriculture

CAST
COUNCIL FOR AGRICULTURAL SCIENCE AND TECHNOLOGY
Headquarters: Agronomy Building, Iowa State University, Ames, Iowa 50011, Telephone 515-294-[illegible] or [illegible]

American College of Veterinary Toxicologists
American Dairy Science Association
American Forage and Grassland Council
American Meat Science Association
American Meteorological Society
American Phytopathological Society
American Society for Horticultural Science
American Society of Agricultural Engineers
American Society of Agronomy
American Society of Animal Science
Association of Official Seed Analysts
Council on Soil Testing and Plant Analysis
Crop Science Society of America
Entomological Society of America
Institute of Food Technologists
North Central Weed Control Conference
Northeastern Weed Science Society
Poultry Science Association
Rural Sociological Society
Society for Range Management
Society of Nematologists
Soil Science Society of America
Southern Weed Science Society
Weed Science Society of America
Western Society of Weed Science

March 26, 1979

Dr. Julian Davies
Department of Biochemistry
University of Wisconsin
Madison, Wisconsin 53706

Dear Dr. Davies:

Now that you have had an opportunity to talk with Drs. Pendleton, Binning, Lower, and Niedermeier, staff members at the University of Wisconsin representing the American Society of Agronomy, the North Central Weed Control Conference, the American Society for Horticultural Science, and the American Dairy Science Association on CAST's board of directors, we should like to put in writing the alternatives they discussed with you. As your fellow staff members explained, we offer you additional alternatives that we hope you may find an acceptable basis for completing the work on antibiotics in animal feeds with inclusion of the input on development of resistance to antibiotics. These alternatives have been discussed with Dr. Virgil Hays, chairman of the task force on antibiotics in animal feeds.

The first alternative is that you take the responsibility for the section on development of resistance to antibiotics comprising pages 15 through 90h in the draft of September 21, 1978. You and any of your microbiological colleagues appointed to the task force who wish to serve with you will be listed as authors of that portion of the document. If you wish, a statement may be added that you take no responsibility for the remainder of the manuscript or something of that nature that may suit your wishes. You may wish to nominate an editor of your own choosing, subject to our approval (for financial reasons only -- we expect to pay the editor for his services). A knowledgeable editor could relieve you of much of the work. Although we would prefer that the text be simplified to avoid use of the many technical terms that would not be understood by the target audience, the only provisions on which we would insist would be that the section contain no recommendations or other statements that could be interpreted as lobbying and that it be in final shape and in our hands no later than November 30.

The second alternative is the same as the first except that you would be listed with Dr. Hays as cochairman of the task force.

The third alternative is the same as the first except that the material now comprising pages 15 through 90h in the draft of September 21 would be published as a separate publication.

All the alternatives listed in my letter of January 22 are still available except for the trip to Europe. Dr. Visek is now making arrangements to go on his own in an attempt to obtain the information.

The report on antibiotics is an important one, and we expect to be sponsoring a press conference at the time of release. If you participate in preparing the material on resistance under any of the alternatives listed, we would expect to call on you to participate in the press conference.

I understand from your colleagues at Madison that you expressed concern about the content of the sections of the report that were not written by your group. We derived the same message from your joint memorandum dated February 21. As I indicated earlier, comments from all task force members are solicited on the entire manuscript. Although Dr. Hays informs me that he has received no written comments from any of your group on any part of the draft of September 21, 1978, such comments are still acceptable, whether or not you participate in the final publication(s) in any other way. The specialists in the various areas are expected to pay attention to comments on their respective parts and to make such adjustments as seem appropriate, but the specialists must have the final responsibility for the subject matter in their own areas.

We appreciate the cordial reception you accorded your colleagues there at the University, and we hope you will find one of the alternatives mentioned here to be acceptable. If you think a meeting with Dr. Hays and me would be helpful, we shall be glad to meet with you in your office or elsewhere. If you wish to discuss anything with us by telephone, please call me collect at 515-294-2036, or call Dr. Hays at 606-258-2686. We look forward to hearing from you.

Sincerely,

Charles A. Black

Charles A. Black
Executive Vice President

cc: Dr. J. W. Pendleton
Dr. L. K. Binning
Dr. R. L. Lower
Dr. R. P. Niedermeier
Dr. V. W. Hays

UNIVERSITY OF WISCONSIN-MADISON

COLLEGE OF AGRICULTURAL
AND LIFE SCIENCES

Department of Biochemistry
420 Henry Mall
Madison, Wisconsin 53706 USA
Telephone: 608/262-3026/262-3040

March 29, 1979

Dr. Charles A. Black
Council for Agricultural Science and Technology
Agronomy Building
Iowa State University
Ames, IA 50011

Dear Dr. Black:

Thank you for your letter of March 26th. I fear that you have the advantage over me since I was unaware until now that my "informal" discussion with Drs. Pendleton et al. was in fact an official delegation from CAST. I was asked to discuss my dissatisfaction with the CAST Task Force on Antibiotics in Animal Feeds and I do not remember that I was presented with "alternatives" during our conversation. At no time was I informed that the group was other than concerned colleagues who were interested in CAST's activities and procedures and who wanted to discuss these matters with me.

We did discuss what approaches might lead to an accurate and complete report of the question of antibiotics in feed, but I was not aware that my colleagues were representing CAST, that they had an official capacity in questioning me about my involvement with the Task Force, or that they would be communicating the substance of our discussions with you.

I hasten to add that Dr. Pendleton and his colleagues in no way attempted to convince me of the error of my ways and were in all repects most courteous, apart from the fact that they did not inform me that the meeting was requested for your benefit (CAST) and not as I had believed, for their personal information and enlightment in view of the recent public criticism of CAST.

I am, to say the least, displeased by this state of affairs which seems to have been somewhat devious. With respect to my future participation in the CAST Task Force or any of the affairs of this organization, particularly in light of this latest episode, I stand by my resignation made in our joint letter of February 21st and have no intention of revising this position, or of accepting any of your "alternatives".

Yours sincerely,

Julian Davies

Julian Davies

jmk

cc: Dr. J. W. Pendleton
Dr. L. K. Binning
Dr. R. P. Niedermeier
Dr. R. L. Lower
Dean Hougas
R. Curtiss III
R. Hovick
M. J. Haas
V. Hershfield

Enclosure

A reading of the thoughtful and thorough article on CAST in the January 1979 issue of *BioScience* has prompted me to relate certain aspects of my recent experience with that organization in connection with its antibiotics in animal feeds task force (AFTF).

This task force was convened in May 1977, shortly after FDA Commissioner Donald Kennedy announced his decision to limit the use of tetracycline and penicillin as feed additives. I accepted the invitation to serve on the AFTF, hoping to be able to contribute because of my long experience with the study of antibiotic resistance in bacteria. The project seemed off to a good start, since several respected biologists were on the task force, and its charge, as drafted by Charles Black, was well-drawn.

The first hint that AFTF might be less than neutral was the package of materials sent to the members prior to our first meeting. This package contained Commissioner Kennedy's statement, a summary of the FDA position, and a collection of reprints of articles advocating antibiotics as feed additives by only two individuals: Thomas Jukes, who is credited with the discovery of antibiotic growth promotion and is a staunch advocate of unrestricted feed additive use of antibiotics (and other chemicals), and Jack Kiser of American Cyanamid, the major supplier of tetracyclines as feed additives.

The second hint was the title of an outline by Virgil Hays, the AFTF chairman, prepared to guide the formulation and execution of the task: "Safety and Efficacy of Antibiotics as Feed Additives, With Special Reference to Tetracycline and Penicillin." Although we were given to believe that deliberations and report writing of the AFTF would involve no more than a single two-day meeting—it has since become clear that this is the usual mode of operation for CAST—before very long we could see that we were facing a monumental task. There was a veritable mountain of relevant literature, in all possible languages and with all possible degrees of accessibility.

Four of my colleagues and I, the so-called "plasmid group," took this task very seriously and set about spending the better part of six months becoming familiar with the available material, conferring with various authorities, and writing our carefully researched and documented reports. Not so the rest of the AFTF members, who were presumably accustomed to the usual, highly superficial CAST format. Those who prepared anything did so in a cursory and offhand manner; several did not prepare anything until after the second (and final) AFTF meeting. This material, of course, was not discussed by the group.

Nevertheless, Black put the heat on Hays to produce an "interim summary" after the second meeting, even though the work of the AFTF had progressed to nowhere near the stage of summarization. This "interim summary," then, was railroaded through so CAST could have input into the FDA hearings on its proposed ban, which were rapidly approaching. The summary contained major sections that had never been presented, let alone discussed, by the AFTF. In addition, it attempted to water down any conclusions that a reader might have reached about the health hazard of antibiotics as feed additives.

At this point, it became clear to most of the plasmid group that the AFTF had been convened for the implicit purpose of providing a document to counter the FDA proposal. This document was to be published widely, sent to members of Congress, and used as industry ammunition in FDA hearings and the court battles that were anticipated. It finally dawned on us that we would be unable to prevent our being used to make legitimate the report of a group already under suspicion of being not an open and neutral fact-finding organization, but rather an advocate of the chemical industry's position on chemicals in agriculture.

Matters went from bad to worse. Following a TV documentary on antibiotics in animal feeds, CAST set up a second task force, also headed by Hays, consisting of four members of the AFTF (none, needless to say, from the plasmid group). The second task force operated in the usual CAST manner, meeting once and issuing a report that strongly attacked the TV show. This placed CAST on public record as advocating the unrestricted use of antibiotics as additives before the report of the AFTF was even nearing its final draft form.

Somewhat later, a draft of the proposed AFTF report was circulated, containing major sections that had never been presented to the group as a whole. The bulk of this new material involved estimates of the economic benefits of feed additive use of antibiotics, estimates that are predicated on assumptions that I, at least, regard as patently false. Additional new material included a long section defending the use of prophylactic antibiotics in human medicine, implying that if it works for humans, what is wrong with using it for animals? In fact, most experts in the treatment of bacterial infections in humans are convinced that attempts at wholesale antibacterial prophylaxis are not only useless, they are positively disastrous in humans—except in carefully selected situations—since they encourage the development and spread of resistant populations of pathogenic bacteria.

As a result of all these considerations, the entire plasmid group resigned en masse from the AFTF last December, and another AFTF member later joined us in this resignation. It seems ironic that there are indications that CAST was making a genuine attempt to achieve at least a modicum of neutrality in this task force, with representatives who did not have prior commitments on the issue in question. The sad thing is that, try as it might, CAST was unable to carry it off; its true position was simply too strong to survive the attempt.

RICHARD NOVICK
Department of Plasmid Biology
Public Health Research Institute
New York, NY 10018

Features and News

Agriculture's Strange Bedfellows:

CAST-Industry Tie Raises Credibility Concerns

The Council for Agricultural Science and Technology (CAST) calls itself a "consortium of 25 scientific societies dedicated to making available sound information related to food and agriculture." CAST was formed in the early 1970s to bring the arguments of agricultural scientists to the realm of political and regulatory decision making—arguments that CAST proponents thought were either missing or overpowered by exaggerated concerns for the environment.

CAST bases its scientific credibility on the traditional scholarship represented by its 25 independent member societies, whose names are displayed prominently on all CAST reports, news releases, and letters. Despite its reliance on certain time-honored scientific conventions, CAST operates in unorthodox fashion, routinely producing scientific consensus statements on controversial issues with a force and speed rarely seen in other scientific organizations.

There's another side to CAST not displayed in its literature. In addition to the 25 societies, more than 200 agribusiness corporations and industrial trade associations belong to CAST, and they provide 57% of its operating budget. And in its public postures, CAST takes a pro-industry stand: CAST defends all pesticides under public scrutiny—aldrin and dieldrin, chlordane and heptachlor, dioxin and DDT—as safe; exonerates such controversial food additives as nitrites in cured meat and DES in cattle feed; and denigrates alternative forms of commercial agriculture such as biological pest control.

This posture is significant because CAST describes itself as an objective educational group of independent, unbiased scientists. In many circles, that's how it is perceived. "The Brookings of the agricultural vote" is the way one congressional staff member, a noted environmentalist, described the group in what he admitted was an impression based mostly on hearsay. "They're very reputable, and they do good scientific work," added his peer on the House agriculture committee, comparing CAST to the National Academy of Sciences as a "good source of data."

But some government and congressional officials who have worked closely with CAST see it as something other than an objective think tank. "We turn to CAST when we want a particular viewpoint, the way we would turn to the American Farm Bureau," say Peggy Wheeler, an aide to Rep. George Brown (D-Calif.) of the House committees on agriculture and science and technology. "We are usually in opposition, but we ask them for input when we want a perspective that is pro-agribusiness, pro-pesticides, pro-expansion of farms."

CAST Money

A look at CAST's balance sheet, and a review of its method of issuing reports and etching them onto the public record, reveals the presence of industry money behind almost everything CAST does. Based on the number of members from the agricultural sciences, the 25 scientific societies that affiliate with CAST pay dues of up to $5,000 a year. Eight CAST society members also belong to the AIBS: American Phytopathological Society, American Society for Horticultural Science, American Society of Agronomy, American Society of Animal Science, Entomological Society of America, Poultry Science Association, Society of Nematologists, and Weed Science Society of America.

If pushed, CAST officials will admit to other, less scientific categories of membership: supporting members and sustaining members. The supporting members, which now number about 115, are agricultural corporations that pay dues of up to $5,000 a year based on sales of agricultural products. These are the companies that manufacture the pesticides, fertilizers, herbicides, additives, and other chemicals that are the subject of CAST reports, press releases, congressional briefings, and film clips—chemicals that CAST almost invariably concludes are not a significant threat to human health. They include such companies as American Cyanamid, Dow Chemical, International Multifoods, Mobil Chemical Company, Ozark Fertilizer, Stauffer Chemical Company, and Transvaal, Inc.

Sustaining members are mostly agricultural trade associations, whose annual dues are $50 for regional groups and $100 for national organizations. Among the more than 125 sustaining members are American Meat Institute, The Fertilizer Institute, National Canners Association, National Grange, National Pest Control Association, Potash Institute, Sulphur Institute, and Roses, Inc.

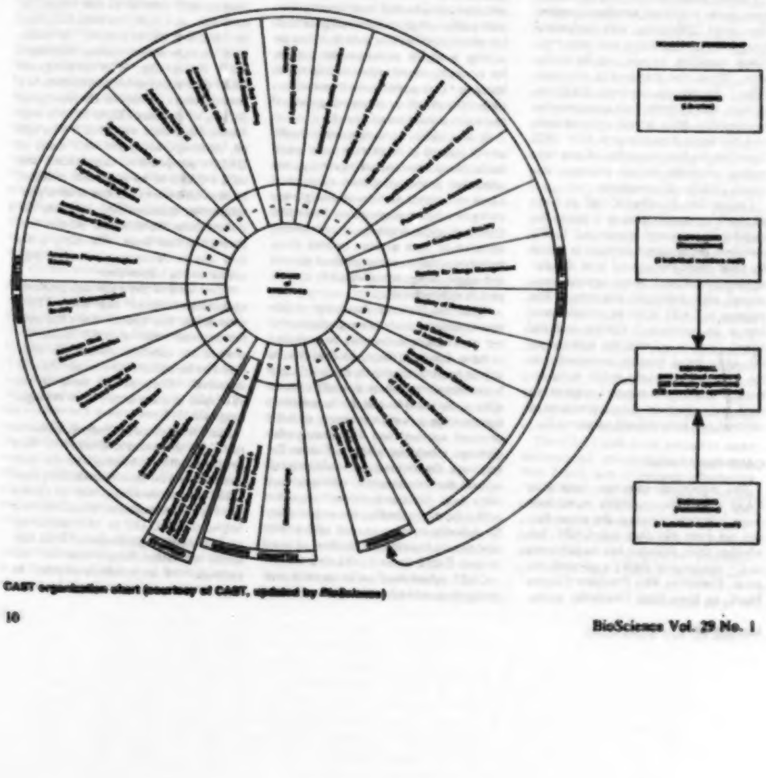
These two categories, along with a catch-all category of "grants-in-aid" from such companies as AgWorld, Merck and Company, National Agricultural Chemicals Association, and Ralston Purina, provided $166,500 of CAST's $292,500 operating budget in 1978. The 25 scientific societies of CAST's self-description accounted for just $36,000, or 12% of the year's budget. The remaining $90,000 (31%) came from individual members, bank interest, and sales of a CAST directory of agricultural scientists.

Even these figures don't tell the whole story. Industry money funnels not only *to* CAST but *around* it, in the form of corporation-sponsored projects and events staged to publicize CAST reports favorable to industry. The magnitude of this involvement is impossible to gauge, but it has taken such forms as a Dow Chemical-sponsored press conference and Capitol Hill briefing on 6 September 1978 for CAST's phenoxy herbicide report (which found Dow's 2,4,5-T of no risk to humans); sponsorship of CAST's five annual national "food safety" phone-ins (the most recent held on 8-9 November 1978) by the National Agricultural Chemicals Association, which cost NACA at least $40,000 in 1977; and production of a 50-second television "newsclip" featuring one CAST scientist describing what risk nitrogen fertilizers might have to the ozone layer (his conclusion: unknown, but probably no higher than the risk from nitrogen-fixing legumes), sponsored by The Fertilizer Institute.

Although there is nothing unusual about industry promoting scientific reports favorable to its products, these industry projects and events appear in CAST's name, not in the name of the industrial sponsor. However, in response to direct inquiry, the sponsor's identity is revealed. When Dow sponsored a round of media interviews with the author of the CAST phenoxy herbicide report last year, for example, at least one AP reporter who was invited to interview the task force chairman was never told of the Dow connection until after the interview. Even then he had to press the New York City publicist who set up the meeting to find out that Dow was paying for her services.

CAST Members

Then there is the matter of proportion. The AIBS has 9 industry members and



CAST organization chart (courtesy of CAST, updated by BioScience)

55 member societies; CAST has more than 200 special interest members and just 25 scientific society members. Moreover, CAST officials, while aware of the appearance of impropriety in this imbalance, are continuing an aggressive push to expand the market further. Industry sponsorship was first sought in 1973, a year after CAST formally incorporated, when a CAST-industry meeting was held in the Deere and Company headquarters in Moline, Illinois.

Six years later, this money is still being solicited. "The potential for increased support from corporations, which constitute the supporting members, is considerable," past president Bart Cardon, chairman of the board of Arizona Feeds, told the CAST Board of Directors last February. "Funding from this source is essential to CAST operations. At the same time, however," he warned, "supporting members form the group that is most suspect in the eyes of critics."

Cardon suggested stepping up recruitment in the individual member category, then about 2500-strong, with representatives from both industry and academia. These members, he said, are far preferable "from the standpoint of credibility." Despite his cautions, CAST recruiters also embarked on an aggressive membership drive among corporations, and between January and July 1978 signed up the largest number of new supporting members in any previous six-month period—18 companies.

Cardon has described CAST as "not so much an organization as a means for marshaling personnel resources." CAST members get no direct services in return for their dues; the reward is in the dissemination of task force reports consonant with members' interests. "The purpose of CAST is not to provide services to its members," Cardon told the board, "but to provide the services of the agricultural science community to the government and the public in the interest of promoting reasoned solutions to food- and agriculture-related problems of national and international concerns."

CAST Task Forces

The essential question regarding CAST's scientific credibility is not how many industrial members the group has, and not even why they join CAST, but whether their presence has an influence on the outcome of CAST's scientific reports. Executive Vice President Charles Black, an Iowa State University agronomist, thinks CAST's method of support through industrial and trade group members actually keeps the organization more scientifically objective than it would be if it relied on government and foundation contracts and grants for research support. "What we do, we decide ourselves," he says. "When you're in the grant business, someone else decides."

"Everyone who is a member of CAST, in all classes, pays his dues but doesn't have anything to say about what is done," Black continues. (Society members, of course, have some say through representatives on the board.) "In the grant system, the people who give the grants are the ones who decide what research is done."

Many other scientific groups, the AIBS included, have industrial members and cosponsor workshops and other events with special interest groups. But the other scientific organizations are aware of the tension between corporate involvement and scientific objectivity, and they tend to deal with that tension with a series of procedural safeguards often missing in CAST activities. When assessing a highly controversial subject, for example, these organizations try to balance their panels and committees with representatives of opposing views if neutrality cannot be achieved.

At the AIBS, a "competency coefficient" is used to measure a panel member's particular expertise—a system which has proven of special value when a task requires a variety of disciplinary backgrounds in a single panel. The AIBS does not allow granting or contracting agencies to have a voice in who is selected to serve on committees or panels, and agencies are not allowed to participate in deliberations.

When the National Academy of Sciences tackles a study of a complicated issue on which scientists can be expected to have firm and disparate loyalties, it strives toward objectivity by selecting a broad-based committee (usually chosen after a nationwide call for nominees), representing a wide spectrum of both personal opinions and disciplinary allegiances; allocating plenty of time for meetings, discussions, and reworkings of several draft documents, with meetings often held "in the sunshine" as open public forums; affording the opportunity for minority opinion as part of the final report; and instituting a method of peer review. CAST doesn't work that way.

CAST prides itself on its rapid report production, and takes many shortcuts in the name of "quick and timely" statements on a given policy issue. In order to facilitate arriving at a consensus on each of the controversial topics the group tackles, CAST deliberately excludes "extremists" from all its task forces. An extremist, to CAST, has been described as "anything left of neutral" by James Witt, an agricultural chemist at Oregon State University. Witt investigated CAST operations as his contribution to a heated debate within the Entomological Society of America (ESA) in 1976 over whether to affiliate with CAST. Witt said no. Although he agrees with many of CAST's pro-pesticide conclusions, and joined CAST as an individual member, he says ESA doesn't belong in an organization that systematically excludes dissidents from the scientific debate. Balancing the task force, Witt says, is the only way to circumvent individual prejudices and to still critics.

Charles Black

"You have to put a few anti-pesticide spokesmen in there," says Witt. "That's what keeps you honest; that's the anvil the hammer beats against." If the dissenters are carefully chosen, he adds, they can be constructive rather than obstructive. "They can be there to rub your nose in some facts you've managed to ignore."

But CAST's modus operandi leaves no room for dissenters. Executive Vice President Black hand-picks the task force, based on recommendations from CAST society members, with an eye toward speedy consensus. Black, 63, who helped found CAST in 1970 and is becoming increasingly immersed in its day-to-day operation, hasn't time for "extremists." "They just cause trouble," he says. "They're unwilling to compromise, to listen, to allow as how anyone but themselves can have a point of view."

Although nominations are made by the Board of Directors—comprising 39 representatives of CAST's 25 society members, 4 national officers, 4 ex officio members, and 4 representatives of individual members—the final choice of a task force and its chairman rests with Black. He also decides which disciplines should be invited to offer nominations. "Fortunately," Black says, "we've been spared the problem" of receiving "way-out" nominees, since CAST directors "don't recommend people with their heads in the clouds; they want people who represent the real subject matter, not some minority offshoot." If Black overlooks a discipline to participate on the task force, not much can be done about it unless the discipline has a representative on the CAST board who tells Black early enough that they want to be included. The result: a distinct parochialism on CAST task forces, with a heavy leaning toward disciplines that are part of CAST's inner circle.

Missing from most of these groups are toxicologists, biomedical researchers, and epidemiologists—a serious flaw, since most reports deal primarily with human risk assessment. Thus, animal scientists, agronomists, and plant pathologists, who dominate the CAST board and its task forces, are often asked to make proclamations about human health for which they may be ill-equipped. The result is that many CAST reports dismiss problems that baffle clinical researchers, such as dose-response curves for carcinogens, with an almost startling equanimity.

"Controversial issues are presented as concluded," observes Witt of ESA. "An example is the issue of whether there is a no-effect level or threshold level for carcinogens. There is a lively controversy on this point in toxicology, partly because the art of extrapolating animal data to humans is in its infancy, but the issue is presented some places in [CAST] documents as if it were concluded." One way CAST does this involves ridiculing the no-threshold theory by calling it "the one-molecule hypothesis," which implies that if there is no safe dose of a carcinogen, however small, then even one molecule of a carcinogen must be able to induce cancer.

The CAST task force reviewing the safety for humans of DES in animal feed is an example of what can happen in the absence of the appropriate experts—in this case, food safety toxicologists. The panel, consisting primarily of animal scientists, food scientists, and agricultural economists, concluded that "natural dietary estrogens far exceed the residues in food from use of estrogen in livestock production. Hence, it is clear that DES residues cannot play any significant role in endometrial cancer." The group also concluded that estrogen therapy has not been linked to breast or endometrial cancer, and that "toxicity is a matter of dosage. All substances in large enough doses are toxic; in small enough dosage they show no significant activity" and thus cannot cause cancer.

Had there been different scientists on the CAST task force, says one FDA official who reviewed the DES report, the conclusion might have been different. The aim of veterinary scientists, the official says, "is to serve their client—a man with a sick animal—and their orientation is toward wanting weapons that keep that animal from becoming sick." Food safety toxicologists, not animal toxicologists, should have the last word on human risk assessment, the official continues, and they would tend to be far more conservative in the level of contamination they would accept.

Charles Black is able subtly but surely to direct the tenor of the CAST report not only by selection of task force members but through other means as well. It is he who puts forth a charge to the group, giving them a specific set of issues to address. And it is he who puts them under tremendous time constraints in the interest of instant consensus.

Task forces usually meet only once, if at all, for two or three days, and do follow-up work by phone, mail, or proxy. Most of the report writing is delegated to one person—usually the chairman, whom Black selected. According to Witt, these ground rules "diminish objectivity, in that much work must be done in isolation, and the chairman is responsible for organizing and integrating a mosaic of reports from individuals with a minimum of opportunity for discussing different points of view, interpretations, and opinions."

Final editing of the task force report is also handled by Black, who says his blue-penciling is limited to improving writing style and eliminating quasi-lobbying statements. Recently, though, his editing has become a bit more heavy handed. A CAST task force on antibiotics in animal feed—one Black didn't have time to select personally when it began work in 1976—has been plagued by controversy between two camps: the agricultural scientists on the one hand and the bacteriologists on the other. The controversy has been heated, Black says, and he recently tried to smooth over the jagged edges and fashion a consensus document to please everybody.

It may please nobody. If the bacteriologists insist, Black explains, they can sign their names only to the section they agree with, and the antibiotics-in-feed report will be issued with a dissenting view—a first for CAST. "But I doubt it will come to that," he adds.

Criticism from Outside

The well-greased mechanism of task force selection and rapid report production, under Black's guiding hand, leaves CAST open to criticism from the scientific community. One of the most vigorous critiques came from FDA in 1977, during a series of hearings on the use of DES in cattle feed. The agency called the CAST report on the topic—which said DES residues in meat were less harmful to humans than naturally occurring estrogens in wheat germ and green vegetables—"a purportedly scientific document which in fact is a collection of conclusions by a number of cattle industry-oriented people, followed by a list of disconnected references and appendices." FDA attorney Robert Spiller, who cross-examined several of the report's authors called to testify in behalf of the DES manufacturers, criticized the report for its "circular cites," "phantom references," and contradictory statements, and called the report "a conclusion in search of citations."

James Witt criticized another CAST report on similar grounds. During the 1976 debate on whether ESA should affiliate with CAST, Witt wrote an anti-affiliation article for the *ESA Bulletin*. In it, he examined CAST's report exonerating the pesticides chlordane and heptachlor to find out whether the group seemed in fact to be an objective scientific body. Based on "selectivity in the presentation of data," he concluded it was not.

The CAST task force tended to make unsupported pro-pesticide statements, Witt found, and to present information "in a way that data favorable to the chemical are uncritically idealized, and unfavorable data are exhaustively examined." He criticized the report's reliance on "obsolete" data, citing its "extensive quotations from a 1963 FDA report stat-

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CAST . . .

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ing that neither chlordane nor heptachlor were found in a study of nearly 500 samples of human tissue. In 1965 the analytical methods for these chemicals and their metabolites were not well developed, and the relevant data have been developed since then," he said.

Witt added that the task force had selectively excluded some important, antipesticide information. The report asserted that no experimental evidence existed to support EPA's arguments that chlordane and heptachlor cause cancer at some dosage, and that their metabolites have been found in every citizen in the United States. If the task force members had made one phone call to EPA, says Witt, they would have been directed to 15 scientific citations supporting that view.

Witt does not ascribe to the CAST authors quite the malicious intent in this omission that FDA's Spiller might. To Witt, their failings are human ones. "I don't think anybody set out to build a biased piece," he says. "Rather, they believed certain things to be true, and when the evidence reached that point their mindset told them they'd finished."

Advocacy or Objectivity?

This is a pitfall for advocacy, Witt says, and CAST is an advocacy group. Witt's primary argument against ESA affiliation in 1976 was that a scientific society should have no part in quasi-scientific advocacy. "There's not a damn thing wrong with advocacy groups," he says. "We all join them—Hell, I was a member of CAST!—but let's be very careful to distinguish scientific groups from advocates. They're both valuable, but if you ever get confused about which role you're playing, you lose your credibility and don't serve your constituents well."

Witt's characterization of CAST-as-advocate comes from his review of the group's original purpose, when in 1970 the American Society of Agronomy and other groups of agricultural scientists first thought of banding together. The glue of their liaison, he says, was a common enemy: ecological scientists and environmentalists issuing dire predictions about the health hazards of DDT, other pesticides, and other agricultural chemicals. ASA members and their peers sought a cohesive voice to counter those claims.

"If the genesis of your group is to contradict another group you perceive to be wrong, clearly you per se become an advocate," says Witt. "You may be quite correct in their being wrong, but you're still an advocate."

Your reports, too, become tools of advocacy when topics are chosen to counteract misinformation on the part of your opponents. Topics for CAST reports are agreed upon by the 51-member CAST board or its Executive Committee, often after a congressional or agency request, sometimes in response to proposed regulations, sometimes self-initiated. Once the topic is chosen, Witt's article asserts, "a conclusion has already been reached, otherwise the topic would not have elicited a response from CAST. This is not wrong or bad, but it means that CAST is arguing its case even before it starts to write a report, in many cases."

Witt's argument was that since the CAST perspective carries over into task force selection, assignment of responsibilities, and methods of instant consensus development, ESA should reject affiliation on the grounds that its own scientific reputation would suffer. "Society participation would compromise all of us, minority and majority alike, unless the reports were absolutely and stringently objective and developed minority views," which they were not and did not, Witt wrote. His arguments were rejected by ESA members in a close 1086-802 vote to affiliate with CAST.

If CAST looked like an advocate in 1976, it looks even more like one today. Its barrage of press releases and letters to editors and reporters has grown steadily and has taken on an increasingly strident tone. Charles Black, from his office in the agronomy building at Iowa State (from which he retires this year to devote full time to CAST out of new offices in the ISU student union), is responsible for these releases, photocopies of which are sent to reporters across the country. As founder and prime mover of CAST, Black takes on the press single-handedly and with uncommon zeal. He has written to the presidents of ABC, CBS, and NBC to criticize their anti-pesticide and anti-carcinogen documentaries; to columnist Jack Anderson to debunk his belief in biological pest control; to the editors of *Harpers*, *The New York Times*, *Christian Science Monitor*, and the *Des Moines Register*, protesting articles Black perceived to be misinformed; and, most recently, to the editor of the *Fort Collins Journal*, the campus newspaper at Colorado State, in response to an antipesticide article.

Friends of CAST worry about Black's increasing criticism of media. This weakens CAST's credibility, they say, especially when it leads Black to write letters not only to reporters but to decision makers CAST hopes to influence, such as Secretary of Agriculture Bob Bergland, Assistant USDA Secretary Rupert Cutler, EPA Assistant Administrator Steven Jellenick, and FDA Commissioner Donald Kennedy.

Black's tone in these letters can be caustic: "To judge from your comments, you have personal knowledge of the subject of exposure of the human body to nitrite," he wrote to Kennedy on 6 November, "that should be published in the scientific literature with documentation so it can be evaluated by the scientific community. We hope you will find time to assemble this information for publication." Such sarcasm did not help CAST's case at FDA. Kennedy ignored the November letter, but he called a 17 October letter from Black on the same subject "particularly outrageous" and claimed Black "simply has not looked at the problem" of calculating exposure to nitrite through ingestion of cured meat.

Prognosis

So far, CAST has not followed the advice of its friends, who urge the organization to display the sources of industrial support on all of its literature and to balance its consistently pro-industry task forces with at least a few dissenters. One CAST board member predicts that, unless the quality of its reports improves, CAST could also lose its most important allies—the agricultural deans—as it becomes clear to universities and land grant colleges that contribution to a CAST report is a professional activity not worth the salaried time of their best faculty members.

Whatever its future prospects, CAST has plans. Among the reports in progress are an appraisal of organic farming, a "pesticide-benefit analysis," and a "quality and safety review" of American meat and animal products. Moreover, some CAST officials are still mulling an idea that surfaced in 1970, when the gel of CAST was beginning to set: a National Academy of Agricultural Sciences, to counteract what the group perceives to be too puny a role for agriculture in the current scientific hierarchy.

—Robin Marantz Henig

Scientists Quit Antibiotics Panel at CAST

Academics and animal feeds do not mix

It is difficult to bundle scientific objectivity and public advocacy into the same package, and few people even try to do it. One group that does try recently met with a spectacular failure. It is the Council for Agricultural Science and Technology (CAST), an association of industrialists, farmers, and agricultural scientists.

CAST devotes much of its time to showing the federal government why chemicals used on the farm are less dangerous than someone has claimed them to be. It often presents its arguments in the form of neutral scientific reviews. Because of the inherent tension in its work, CAST lives and breathes controversy, but seems not to thrive on it.

In December seven academic scientists resigned from a CAST task force planning a report on the risks of feeding livestock large but less than therapeutic quantities of antibiotics to promote growth. The Food and Drug Administration (FDA) found in 1972 that the unregulated use of drugs in feeds posed a significant health hazard because it creates an "ideal environment" for the generation of antibiotic-resistant strains of bacteria that may infect humans. Since 1972 the FDA has been trying to regulate the use of antibiotics in animal feed, and up until now, agricultural lobbyists have argued successfully against regulation. FDA Commissioner Donald Kennedy revived the campaign to control drugs in feed in 1977, but Congress intervened in September 1978, ordering the FDA to delay its decision until new hearings and studies have been completed, one of which will be conducted by the National Academy of Sciences. The CAST report was intended for use in these hearings, in congressional debates, and in news briefings, as an objective summary of costs and benefits.

In quitting CAST, six of the scientists signed a sharp letter of protest on 13 December accusing CAST of omitting unfavorable evidence on the risks of drug use from a draft final report, stressing favorable evidence on the benefits, and generally bending science to fit the public relations aims of the organization. Those who signed the letter were Roy Curtiss III, a microbiologist at the University of Alabama and creator of the disabled bacterium used in gene-splicing experiments; Raul Goldschmidt, a colleague of Curtiss at Alabama; Richard Novick, a microbiologist at the Public Health Research Institute of the City of New York; Julian Davies and Michael Haas, biochemists at the University of Wisconsin; and Vickers Hershfield, a microbiologist at the Duke University Medical School. A seventh member of the task force, microbiologist Marvin Bryant of the University of Illinois, resigned in January, joining the protest.

"The microbiological aspects were the whole crux of the problem," said Virgil Hays, chairman of the task force and a professor in the animal sciences department at the University of Kentucky at Lexington. Hays and CAST's executive vice president, Charles Black, recruited the seven experts in antibiotics in 1977 in order to give CAST's work more depth and credibility. As Black put it, "These people were invited to participate because they were specialists in microbiology. We wanted them so that the whole story would be told. We're going to try to keep them in there." When they left, the scientists asked that neither their names nor their research be included in the report, possibly a fatal blow to the paper and to CAST's reputation.

CAST, based at Iowa State University in Ames, was organized in 1972 "to advance the understanding and use of agricultural science and technology in the public interest" and to provide information on disputed issues in agriculture. The group is governed by the members of the 25 scientific societies that belong to it, and it finances nearly two-thirds of its $265,000 annual budget with donations from industrial "supporting members" such as Dow Chemical, American Cyanimid, Eli Lilly, Mobil Chemical, and others. In its policy reports, it maintains a strictly neutral stance, although the conclusions often seem to favor the benefits of using chemicals over the risks. CAST supported the use of the herbicide 2,4,5-T and the use in animal feed of the hormone diethylstilbestrol, for example.

When Black wrote to the scientists who agreed to serve on the antibiotics task force in May 1977, he made it clear that he wanted them to be dispassionate, even bland, in presenting the facts: "You should recognize the arguments on both sides and should keep them in due perspective without leaning too far one way or the other." Black also instructed the experts *not* to make recommendations: "If we write our educational material properly, the persons who read it will be able to appreciate the points we wish to make." Furthermore, he added, if the policy-makers "have reasons for adopting a policy other than the one for which some of us have a personal preference, our subsequent relations with them will be far better than if we had clearly recommended something they did not adopt." Hinting at one's convictions is more politic than stating them plainly.

There is a difference between blandness and objectivity, the microbiologists say, and they feel that their expertise was trampled in the rush to write an "even handed" report favoring the use of antibiotics. Two things annoyed them in particular. One was an impromptu rebuttal to an ABC news documentary on animal feed, given in the summer of 1978 by a CAST task force headed by the same man who headed their own group—Virgil Hays. The rebuttal disparaged the remarks of a microbiologist who appeared in the documentary—Stanley Falkow of the University of Washington—and whom CAST's microbiologists respect. According to Roy Curtiss, "We were confused. Some of us even thought the rebuttal was submitted by the task force we were members of and that we were in part responsible for it." Only later, "in a roundabout way," Curtiss said, they learned that no member of their group had been asked to comment on the ABC documentary, and in fact CAST never consulted any microbiologist—just a few veterinarians. Black commented: "That was a separate project. They had nothing to do with it. They aren't the people who decide what is done" at CAST.

The other complaint was that CAST failed to give the microbiologists' views adequate weight in the preliminary report filed with the FDA in 1977, or in the final draft sent out for a last reading on 4 December 1978. The final draft, according to the letter of resignation, failed to include information presented to the group in November "which we believe is pertinent," and it included other controversial sections "never presented nor discussed by the task force." The paper "contains numerous inaccuracies and is misleading," the letter charged. Curtiss gave an example. In the economic analysis section, CAST calculated that if antibiotics were banned outright it would cost farmers and consumers between $500 million and $2 billion a year. But this estimate is misleading, Curtiss believes, because it does not correspond to what the FDA has proposed. The FDA has approved more than 50 drugs for use in feeds as alternatives to penicillin and tetracyclines, Curtiss claimed, but CAST never considered what it would cost to switch to these. Presumably it would cost less than using no drugs at all.

Black said that Curtiss and the others were not invited to write the whole report—economics and all—just the section on microbiology. He mentioned that the microbiologists had been sent on several trips at CAST's expense to gather evidence supporting their views, that no one had told them what to write, and that, as editor, he had done all that he could to accommodate their late additions to the report. The heavy editing was necessary, he said, because "time was marching on" and overlapping segments had to be cut by someone. He insisted that there is still time for revision, and cited a letter dated 22 January, in which he asked the dissidents to rejoin the group. In the letter, Black offered several enticements, including a trip to Europe for one of the microbiologists to gather more data. Black's most generous proposal was to allow the dissidents to remain members of the task force, but to print their names only under the section of the report they wrote. In addition, he offered to publish their criticism of other sections.

The microbiologists seem in no mood to accept. Curtiss said the likelihood of his changing his mind was "very remote." Novick said he "absolutely would not" rejoin. Others, including Hershfield and Davies, said they were disillusioned and discouraged. "It left a bitter taste," Hershfield said, "They were trying to refute our arguments with what we considered to be fallacious statements." Like others, she was put off by what seemed a dull, inflexible bias in favor of industry in the meetings. When asked why they had agreed to work for CAST in the first place, the scientists gave a common answer. We were naïve, they said.

This is a plausible explanation, but problematic. CAST has been accused of bias before, as it was when members of the Entomological Society of America waged a losing campaign against joining CAST 3 years ago (*Science*, 20 August 1976). The news of that quarrel must never have reached the seven microbiologists. Although CAST's reputation for scientific integrity apparently survived that earlier embarrassment, it will have a hard time surviving the present one.—ELIOT MARSHALL

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Decrease of Drug Resistance in *Salmonella* in The Netherlands

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Since 1974, tetracycline resistance in salmonellae of human and porcine origin has decreased nation-wide in The Netherlands. This decrease has coincided with the ban on incorporation of tetracycline in animal feeds.

Since 1959, all salmonella strains (about 30,000 per year) sent for serotyping to the National Salmonella Centre have also been screened for drug resistance (3, 8, 9). The majority of the strains (about 90%) that were found to be resistant to one or more drugs were typed as *Salmonella typhimurium*. About 60% of all human isolates and nearly 80% of all porcine isolates belong to this serotype. *S. typhimurium* may therefore serve as an indicator of the emergence of drug resistance in salmonellae in The Netherlands. The major changes in drug resistance in salmonellae concerned tetracycline (Tc) resistance. This note will therefore be limited to a description of the incidence of Tc-resistant *S. typhimurium* isolates.

Strains were tested for resistance with the tube dilution method, and were considered as Tc resistant when the minimum inhibitory concentration was ≥20 μg/ml (5). The main features of the emergence of Tc-resistant *S. typhimurium* isolates in humans, pigs, calves, and cattle are presented in Fig. 1. Tc-resistant isolates from humans and pigs were rare in 1959–1960, peaked at 40 to 50% in 1963–1966, and peaked again at 80 to 90% in 1973. After 1973, the incidence of Tc-resistant *S. typhimurium* isolates from these sources dropped.

With the introduction of a revised phage-typing system for *S. typhimurium* in 1971 (2), a comparison was made between the phage type and the antibiogram of each *S. typhimurium* strain (6, 7). Some relevant results are outlined in Fig. 2. The predominant *S. typhimurium* phage type in 1971–1974 was type 505; strains of this phage pattern were predominantly Tc resistant, due to the presence of a particular Tc resistance plasmid, pRI20 (5). In humans and pigs, the incidence of type 505 strains increased during this period. After 1974, the incidence gradually decreased. The percentage of Tc-resistant phage type 505 strains increased from 76% in 1971 to 99% in 1973 and then gradually dropped to 72% in 1978. A similar decrease of Tc resistance was also observed in *Salmonella panama* from human and porcine sources, but in this serotype the resistance dropped from about 55% in 1972 to 2% in 1977. In pigs and humans, Tc-resistant *S. typhimurium* strains were gradually replaced by Tc-susceptible strains with other phage patterns, such as phage types 650 and 260.

In calves, the incidence of Tc-resistant *S. typhimurium* isolates differed from that in pigs and humans. The absolute numbers of type 505 isolates remained rather constant from 1971–1978 (Fig. 2). From 1972 on, multiply drug-resistant strains with phage type 201 were found in increasing numbers. Their number dropped after 1974, but increased again in 1978. In 1977 and 1978, many multiply drug-resistant *S. typhimurium* strains with phage types other than 201 and 505 were isolated from calves. A small percentage (5 to 12%) of these strains belonged to phage types 204 and 193, which have been described in several outbreaks of calf salmonellosis in England (4). From 1975 on, an increasing number of multiply drug-resistant *Salmonella dublin* strains was encountered in calves. Multiply drug-resistant *S. typhimurium* and *S. dublin* strains cause a severe salmonellosis in calves. Such strains will frequently be exposed to therapeutic levels of antimicrobial drugs. This might explain the selection of multiply drug-resistant, virulent strains in calf herds.

Multiply drug-resistant strains were only sporadically encountered in humans. This can be explained by the fact that affected calves either die or, if they reach meat inspection, will not be considered fit for human consumption. The majority of the type 505 *S. typhimurium* strains, however, originate from healthy animals, especially slaughter pigs (1). Such animals pass meat inspection and thus reach the human consumer. In The Netherlands, pork is consumed in larger quantities than calf meat. These facts explain

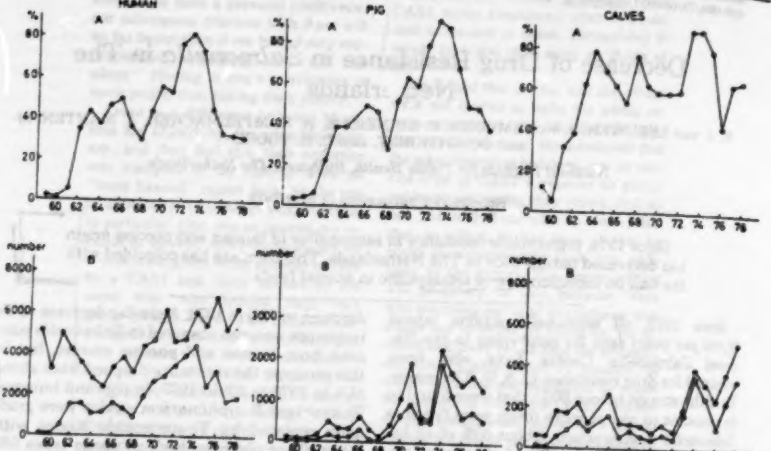

FIG. 1. *Annual figures of Tc resistance among strains of S. typhimurium isolated from humans, pigs, and cattle from 1959 to 1978. (A) Percentage of S. typhimurium isolates resistant to Tc. (B) Number of isolates investigated (●); number of Tc-resistant isolates (○).*

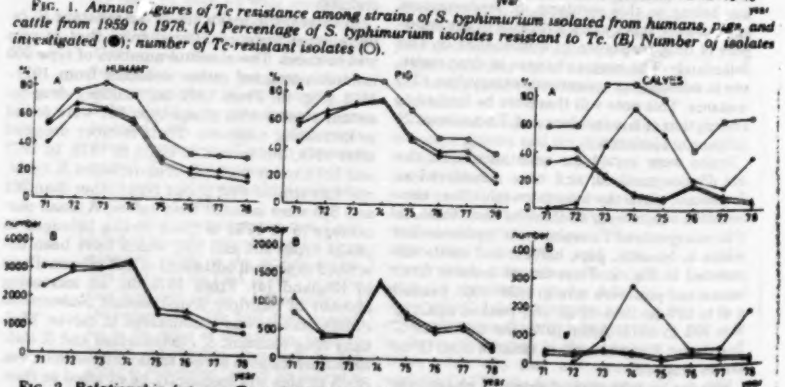

FIG. 2. *Relationship between Tc resistance and phage type of strains of S. typhimurium isolated from humans, pigs, and calves and cattle. (A) Percentage of isolates resistant to Tc (□); percentage of isolates of phage type 505 (△); percentage of isolates of phage type 505 and resistant to Tc (○); percentage of multiply resistant isolates of phage type 201 (●). (B) Absolute number of strains investigated; number of type 505 strains (△); number of Tc-resistant type 505 strains (○); and number of multiply resistant type 201 strains (●).*

the concurrence of the decrease of Tc-resistant salmonellae in pigs and humans. In January 1974, the European Common Market regulations on the use of antibiotics for nutritive purposes came into force in The Netherlands. Tetracyclines, which had been used for growth promotion in increasing quantities since the early sixties, were now no longer permitted for this purpose. Casual monitoring of animal feed since 1974 indicates that the ban has been executed. On the other hand, there is no indication that the use of Tc on veterinary prescription has been changed since 1974. The coincidence of discontinuing the use of tetracyclines for growth progestion on one hand, and the nation-wide decreased incidence of Tc-resistant *S. typhimurium* and *S. panama* strains in pigs on the other hand, are highly suggestive for the role that nutritive doses of Tc have played in the emergence of Tc-resistant salmonellae in pigs and humans.

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Why has Swann failed?

Current regulations on the use of antibiotics in animals bred for food have failed to prevent the rapid emergence of multiple drug resistance in *Salmonella typhimurium* in bovines in Britain. Presenting convincing evidence for this, Threlfall and his colleagues (p 1210) show that two types of multiresistant salmonellas that first appeared in bovines in 1977 were identified in 290 cases of human salmonellosis in Britain up to the end of 1979. During 1979 a new variant appeared and affected calves on at least 50 farms in the south and south-west of England, spreading to Cambridgeshire and Yorkshire through the distribution of infected animals. This latest multiply-resistant strain was induced by the new use of trimethoprim in bovines. Twenty human infections with this strain had been identified by the end of 1979. These developments must be a cause of real concern to doctors: the latest variant is resistant to ampicillin, chloramphenicol, kanamycin, streptomycin, sulphonamides, tetracyclines, trimethoprim, and furazolidone. If such a strain causes septicaemia or other extraintestinal lesions in a patient most antibiotics will be ineffective. In human salmonellosis caused by the first two of the multiresistant types most of the patients suffered only mild-to-moderate enteritis, but some had severe diarrhoea persisting for several weeks; one elderly patient died, seven had invasion of the blood stream, and one 3-year-old infant died of septicaemia. Obviously we cannot dismiss the problems as unimportant, particularly as cases have not been confined to farming families and the multiresistant strains have evidently entered the food chain.

Legislation was enacted, as a result of the Swann Report,[1] precisely to prevent such developments. Antimicrobial substances (mainly antibiotics) were classified into two categories, "feed" and "therapeutic." Those in the feed category had either no therapeutic role or very little, and were available for use in animal feeds without prescription. Therapeutic antimicrobials could be prescribed only by a medical or a veterinary practitioner, and the regulations emphasised that the veterinarian was to prescribe a therapeutic antimicrobial only if he had the animals under his care. Suggestions that chloramphenicol might be prohibited from veterinary use were resisted; they were not recommended by the Swann Report on the grounds that strict limitations on its use were to be set out and that these would be observed by a responsible profession anxious to maintain good ethical standards. In an earlier paper[2] Threlfall and his colleagues suggested that the veterinary profession ought to show more prudence in its prescribing habits; and in their present paper they say that "the responsibility to prevent or control drug resistance in *S typhimurium* in bovines in Britain lies with the veterinary profession." But this oversimplifies the matter: members of the medical profession also must accept reproach for their uncritical prescribing of antibiotics. Richmond and Linton[3] conclude that the medical as opposed to the veterinary use of tetracycline seems to have created the main selective pressure for the high incidence of tetracycline-resistant organisms in the human population.

Apart from incautious prescribing, we must look at other factors in seeking to discover why the Swann recommendations have failed in their main objective—namely, preventing the spread of resistant micro-organisms from farm animals to man. The Swann Committee laid considerable emphasis on preserving the therapeutic usefulness of chloramphenicol, and the great increase in chloramphenicol resistance in the agricultural environment is particularly worrying. There are several reasons for the failure. Firstly, the use of other drugs—such as tetracycline, trimethoprim, and probably others used in animals—may encourage the spread of resistance to chloramphenicol as part of the multiple resistance carried by some of the organisms the antibiotics are directed against. Secondly, over-enthusiastic representatives of pharmaceutical firms as well as black market operators may find farmers, including poultry producers, all too ready to sidetrack their veterinarians and to bid for any supplies of prescription-only antibiotics that may become available through irregular channels. Prosecutions may close that door if evidence is forthcoming, and farmers need to be educated out of attempting to diagnose and treat or prevent enteritis by using antibiotics without veterinary help. Thirdly, advertisements in farming papers encourage such attitudes among farmers; this trend needs to be reversed, however delicately and indirectly the hint is conveyed. Fourthly, the long-incubated protein-processing order should have been introduced well before now and made law to reduce salmonella-infected feeds given to animals.

We need an administrative and political reaction to the regrettable discovery that—for whatever reason—the limited regulations based on the Swann Report have failed. Exactly why they failed, and when, may not be easy to discover; but clearly the present state of affairs is unsatisfactory and dangerous and more stringent regulations are needed.

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[1] *Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine (Swann Report).* Cmnd 4190. London: HMSO, 1969.

[2] Threlfall EJ, Ward LR, Rowe B. Spread of multiresistant strains of *Salmonella typhimurium* phage types 204 and 193 in Britain. *Br Med J* 1978;ii:997.

[3] Richmond MH, Linton KB. The use of tetracycline in the community and its possible relation to the excretion of tetracycline-resistant bacteria. *J Antimicrob Chemother* 1980;6:33-41.

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MISSOURI FARM NEWS SERVICE
College of Agriculture and Extension Division—University of Missouri-Columbia
Vol. 69 No. 28
July 9, 1980

July 3, 1980

Dear Editor:

It has been called to our attention that the headline on the story concerned with feeding antibiotics to swine in the July 9, 1980 Missouri Farm News Service does not accurately reflect the contents of the story. The revision at the right provides a more accurate headline.

Cordially,

Dick Lee

Dick Lee, Director
Extension Information

Hog Producers Differ on Effects of Antibiotic Ban

Most Missouri hog producers would come out winners if the proposed ban on antibiotics in livestock feed becomes a fact.

"That's because antibiotics are of most benefit to large scale producers where large numbers of animals are kept in confinement. Disease is more of a problem under these circumstances," said Bill Heffernan, University of Missouri-Columbia rural sociologist.

"Most Missouri hog farms are small to medium, partial confinement operations."

A recent poll conducied by Heffernan and Joel Hartman, another UMC rural sociologist, showed that only 13 percent of those surveyed said they always included low levels of antibiotics in their feeds.

"When we checked the survey results more closely, we found that 80 percent were using antibiotics to some extent. But many more of the small producers felt they could get along without them.

"Of those who said they never used antibiotics in their feed, almost 30 percent said antibiotics were "too expensive"; 19 percent said "we do not think they have any effect"; and 48 percent felt the antibiotics "did more harm than good."

But Heffernan and Hartman figured the key question in the poll went like this:

"If the use of these antibiotics as feed additives was prohibited by law, what would be the effect on your farming operation?"

The response: 21 percent said "serious," 42 percent said "not serious," 26 percent said "no effect" and 11 percent responded "not applicable."

"Over 70 percent of the large producers felt the ban would have a serious effect on their operation. These producers have over $100,000 annual income and earn over half of their farm profits from hogs," said Heffernan.

"The rest of the respondents—which you have to say are more typical of the relatively small hog producer you find in Missouri—really didn't think the ban would have that much effect.

The proposal to prohibit antibiotics in livestock feed, first put forth by the Food and Drug Administration, is currently bring considered by a House subcommittee on Interstate and Foreign Commerce and another on Health and Environment.

THE ECONOMIC EFFECTS OF A PROHIBITION ON THE USE OF SELECTED ANIMAL DRUGS

U.S. DEPARTMENT OF AGRICULTURE
Economics, Statistics and Cooperatives Service
September 1978

INTRODUCTION

Since earliest times man has struggled to develop an abundant and safe food supply. Over time, though, the increased use of chemicals and drugs has played an important part in improving man's ability to increase production, retard spoilage and preserve in other ways the naturally perishable food substances.

These improvements have not come without a cost. Chemicals, once thought to be absolutely necessary for food preservation, are now being implicated as causal agents directly related to human health conditions. As a result, and in an attempt to protect the inherent safety of the food supply, public policies to ban or otherwise regulate the use of a wide variety of animal feed additives are being proposed and debated.

The subtherapeutic uses of some animal drugs are being questioned because of evidence linking resistant strains of certain organisms to the chronic intake of antibiotics. For example, the Food and Drug Administration (FDA) has demonstrated that strains *Pasteurella multocida* and *Pasteurella haemolytica* have developed a resistance to penicillin, streptomycin, sulfonamides and tetracyclines. The development of such resistance, is a serious concern because it makes the use of these antibiotics potentially less effective in dealing with human health problems.

Proposals to restrict the therapeutic and subtherapeutic use of the nitrofurans stem from the finding that these antibacterials produce tumors in laboratory animals. Since manufacturers have been unable to produce an adequate method of analysis to assure the absence of residues in human food, there continues to be doubts whether their use in animal feeds poses a threat to human health.

A potential proposal to restrict the use of sulfamethazine in hog feeding stems from the continued high levels of sulfa residue being detected in pork tissue.

Farmers have used drugs at subtherapeutic levels in raising animals for approximately 25 years. Over the years they have come to believe that such a use (a) reduces the risk of animal disease outbreaks, (b) improves feed efficiency, and (c) reduces condemnations of the final product. In short, while limited scientific evidence is available to either support or refute the notion, the subtherapeutic use of animal drugs is now believed responsible for reducing the unit costs of animal production.

At the request of the United States Senate Committee on Agriculture, Nutrition, and Forestry, USDA initiated this study of the economic consequences of the proposed and potential retrictions on animal drug use. The study focused mainly on the effects such a restriction would have on food availability, food and farm prices, farm production costs, and the level and distribution of farm income.

While the results of this study must be considered as merely suggestive, they do indicate that the economic system would generally be quite resilient to a more restrictive policy on animal drug use. Costs of production, and therefore consumer prices, would increase initially but because the farm-level demand for most livestock products is inelastic, farm prices would increase more than proportionally. As a result, total net revenue to farmers would be initially enhanced. The increased profitability would encourage farmers to expand output in subsequent years and by the fifth year following the restriction on animal drug use, production and prices of most affected species would recover to approximately their baseline levels.

These results do not take into account any changes in the structure of production agriculture that might accompany an animal drug ban. Increased risks associated with feeding poultry and livestock in confinement without the low-level use of animal drugs could make such confinement production systems less viable and change the magnitude of this result. On the other hand, we were not able to measure the effect of changes in management practices that might occur in anticipation of or following the enactment of such a rule. Improved sanitation and pasture rotation could reduce the magnitude of even the first year affects as we have shown them.

The Study

Basic science data are essential to a study such as this. Without good data on the effects of subtherapeutic drug use on feed efficiency, growth rates, mortality and product condemnation rates, it is impossible to develop precise estimates of the economic effects resulting from a ban. The basic science data for this study were obtained from USDA and Land Grant university scientists, veterinarians, others in private business, and professional journals. Most estimates were extrapolated from small scale test results since other data were not available. Most of the data were from tests conducted when the additives were first introduced in the 1950's and 1960's. In many instances there were wide variations in test results making estimates of the changes in production coefficients subject to error. Despite such difficulties, however, it should be emphasized that the best available scientific data were used for this study.

Because the available scientific evidence on the animal production effects of drug use are not conclusive, two levels of drug efficacy were assumed--a moderate and high level. Such a procedure, therefore, provides a range of potential outcomes that likely bracket what could reasonably be expected to occur in reality.

The estimated initial effects on animal production of restrictions on the low-level use of selected animal drugs are shown in Table 1. These data indicate, for example, that the first year cumulative effect of a restriction on the use tetracyclines and sulfa in feeding hogs would be a 4.9 to 17.8 percent reduction in output, depending on what is assumed about drug efficacy.

As the data indicate, use of animal drugs within the same specie was assumed to generate additive effects. That is, banning the use of all four animal drugs was assumed to be equivalent to the cumulative effect of separate bans occurring one at a time. It was also assumed that substitute drugs would not be available for use and that producers would not change management practices in order to effectively circumvent the regulations. While these assumptions admittedly do not mirror what would take place in the real world they make the problem amenable to analysis and allow us to set bounds on the extent of the economic impact.

The economic analysis was conducted assuming both a species-by-species ban of each animal drug and an across species concurrent ban of all the drugs. The cummulative effects of an across species ban were estimated by taking into account the adjustments in production that would occur as a result of cross-commodity effects. For example, the increased demand for beef resulting from higher pork prices was explicitly taken into account. The net effects of an animal drug ban on prices, production and consumption were traced for a hypothetical 5 year period following the ban to indicate whether, and to what extent, there would be long term adjustments to the changed conditions.

Results 1/

The study results indicate that, at least initially, net farm income, farm and food prices, and farm production costs would all increase if the subtherapeutic use of animal drugs were restricted. Farm production costs per unit would increase because animal production is made less feed efficient and because mortality is increased. Farm and food prices would increase because fewer animal units are offered for sale. Net farm income would increase because increases in aggregate costs of production would be than offset by increases in aggregate receipts. This result would, of course, be expected in cases where the demand for a product is relatively price inelastic.

1/ In order to simplify the discussion only the effects of the moderate efficacy assumption are explicitly discussed in this summary. If the high efficacy response is assumed, the pattern of adjustment is identical to that assuming moderate efficacy. However, reductions in output for the affected specie are more pronounced and, as a result, prices are relatively higher. Magnitude changes are shown in the tables attached.

Total net farm income in the first year following the animal drug ban would be about $1.2 billion above the baseline estimate (moderate efficacy). Increases in livestock cash receipts (+2.9%) would more than offset the relatively small decreases in cash receipts from crops (-1.4%). In subsequent years, net farm income would move steadily closer to the baseline estimate. By the fourth period, net farm income would be slightly below the baseline estimate (-1.2%) reflecting primarily the somewhat higher costs of producing about the same total output of livestock product. (Table 2)

Consumer price impacts follow essentially the same pattern as the index of farm prices received. The first year impact on the CPI for food is the most significant (1.2 percent above the baseline estimate). Consumer prices for the livestock products would be affected most. Retail poultry prices would be up 10 percent, beef prices up 3 percent and pork prices up about 4 percent. By the fifth period, slightly higher prices would persist for pork and poultry products, but because of the relatively low weight of these items in the food CPI, there would be almost no change from the baseline food CPI estimate. (Table 3)

Under the assumption of moderate drug efficacy, a restriction on animal drug use implies about a 7 pound per person reduction in the availability of red meat and poultry products. Broiler consumption in the first year is reduced most (3 1/2 pounds per capita); followed by pork (2.8 pounds), turkeys (1/2 pound) and beef (1/4 pound). (Table 4)

Price deviations from the base estimate for both the moderate and high level efficacy are shown in Table 5. In the first year, broiler and turkey prices would be above the baseline estimate by about 12 percent, assuming moderate efficacy. Barrow and gilt prices would be up about 5 percent and fed beef prices would be about 4 percent above the baseline estimate.

By the fifth year, all prices would be relatively closer to the baseline estimates. Broiler and turkey prices would still be higher than baseline reflecting the relatively higher costs of producing poultry products without the subtherapeutic use of the chemicals and drugs.

The study also provides an estimate of the effects of a ban on the use of the four additives in producing dairy products and sheep. The impact of such a ban on dairy producers would be minimal. Such additives are now used at subtherapeutic levels only in the feeding of calves. Study results indicate that costs of producing milk would increase less than 1 cent per cwt. if that use were banned.

Impacts of an animal drug ban on sheep and lamb production would also be minimal. Study results indicate an approximate 1 percent reduction in gross farm receipts to sheep producers if the additives had been banned in 1976. In that year consumers would have paid about a cent per pound more for mutton and lamb and there would have been about 47,000 cwt. less meat available.

Table 1--Estimated Percentage Change in Livestock Product Output from Banning Selected Drugs in Subtherapeutic Uses, Moderate and High Drug Efficacy, Each Species Considered Separately, First Period (1976)[1]

Animal species	Penicillin		Tetra-cyclines		Nitrofurans[2]		Sulfa [3]		Cumulative effect	
	Drug Efficacy									
	Moderate	High	Moderate	High	Moderate	High	Moderate	High	Moderate	High
	Percent									
Fed beef cattle	—	—	-0.4	-0.8	—	—	—	—	-0.4	-0.8
Hogs	—	—	-3.4	-15.6	—	—	-1.5	-2.2	-4.9	-17.8
Broilers	-2.1	-3.8	-6.4	-11.5	0.2	-5.7	—	—	-8.3	-21.0
Egg production	-0.6	-1.0	-1.2	-2.3	0.1	-0.3	—	—	-1.7	-3.6
Turkeys	-1.4	-2.8	-2.8	-4.6	-1.9	-8.7	—	—	-6.1	-16.1

[1] The higher the expected response to a feed additive, the greater will be the reduction in output if the additive is banned.

[2] In poultry, it is possible to get a slight increase in output when nitrofurans are removed from the feed. These circumstances are explained in the appendix material on poultry. A ban on nitrofurans at all levels was assumed.

[3] The major effect would be from the sulfa drugs but would also include the effects attributed to penicillin and the nitrofurans.

Table 2--Percent Deviation from Base Projections of Selected Farm Income Indicators Resulting from a Ban on the Subtherapeutic Use of Animal Drugs, Moderate and High Efficacy

	Period 1		Period 2		Period 3		Period 4		Period 5	
	Moderate	High	Moderate	High	Moderate	High	Moderate	High	Moderate	High
Cash receipts from livestock	2.9	6.7	2.0	5.2	1.5	3.1	0.9	1.7	0.5	1.3
Cattle	3.0	11.3	2.3	8.3	2.0	5.0	1.2	2.4	0.4	1.8
Hogs	0.2	- 3.5	-0.1	- 2.6	-0.0	- 1.3	0.2	- 0.2	0.2	0.0
Broilers	8.4	19.1	5.9	-18.3	5.5	12.2	3.9	8.9	2.9	6.2
Turkeys	2.1	2.6	1.0	1.6	0.4	1.1	0.4	0.8	0.5	1.1
Cash receipts from all crops	-1.4	3.4	-1.1	-2.0	-0.6	-1.1	- .6	-0.9	-0.4	-0.7
Corn	-3.4	- 8.9	-2.7	-3.8	-1.5	-2.4	-1.2	-1.6	-1.0	-1.5
Soybeans	-3.0	- 7.2	-3.0	-5.1	-1.9	-3.7	-1.3	-2.6	-1.1	-1.9
Oil crops	-2.7	-,6.7	-2.8	-4.8	-1.2	-3.4	-1.3	-2.4	-1.0	-1.8
Total receipts from marketings	0.9	2.7	0.5	1.9	0.5	1.1	0.3	0.5	0.1	0.4
Total farm expenses	-0.2	- 0.4	0.3	0.5	0.4	1.0	0.5	1.0	0.5	1.2
Total net farm income	4.7	10.9	1.6	6.6	0.0	1.2	-1.2	-2.0	-2.1	-3.8

Table 3--Percent Deviations from Base Projections of Selected Consumer Price Indexes, Animal Drug Ban, Moderate and High Efficacy

	Period 1		Period 2		Period 3		Period 4		Period 5	
	Moderate	High	Moderate	High	Moderate	High	Moderate	High	Moderate	High
Beef and veal	2.7	10.4	2.2	7.7	1.4	3.4	0.7	1.4	0.0	0.7
Pork	4.5	14.7	3.5	11.8	2.1	7.3	1.4	4.8	1.0	3.2
All red meats	3.2	11.7	2.6	8.9	1.6	4.6	.9	2.4	0.3	1.4
Poultry	10.3	27.6	5.7	15.9	2.6	7.4	2.4	6.5	2.2	5.6
Total, meat, poultry and fish	3.4	11.0	2.4	7.7	1.3	3.9	0.9	2.3	0.5	1.6
Total livestock and products	2.6	8.1	1.8	7.1	1.0	2.8	0.6	1.6	0.3	1.2
Food at home CPI	1.2	3.8	0.9	2.7	0.4	1.3	0.3	0.7	0.2	0.6
Total CPI	0.2	0.5	0.1	0.3	0.1	0.2	0.04	0.1	0.0	0.04

Table 4 -- Estimated Quantity and Percentage Change in Per Capita Production of Beef, Pork, Broilers and Turkeys from Base from Ban on the Subtherapeutic Use of Animal Drugs 1/

	Units	Drug efficacy			
		Moderate		High	
		Period 1	Period 5	Period 1	Period 5
All beef (carcass wt.)	lbs.	- .23	+ .39	- .34	+ .72
Percentage change	Pct.	- .21	+ .36	- .31	+ .67
Pork (carcass wt.)	lbs.	-2.79	- .58	-10.23	-2.10
Percentage change	Pct.	-4.52	-0.85	-16.59	-3.08
Broilers (RTC) 2/	lbs.	-3.44	- .89	- 8.70	-2.26
Percentage change	Pct.	-7.26	-1.61	-18.37	-4.08
Turkeys (RTC) 2/	lbs.	- .59	- .28	- 1.45	- .70
Percentage change	Pct.	-5.94	-2.50	-14.60	-6.26
Total net change	lbs.	-7.05	-1.36	-20.74	-4.34
Percentage change	Pct.	-3.06	- .56	- 9.01	-1.79

1/ Based on 1977 civilian population of 216.7 million.
2/ RTC = "ready to cook."

Table 5--Price Deviations from Base Projections, Resulting from a Ban on the Subtherapeutic Use of Selected Animal Drugs, Moderate and High Efficacy. 1/

	Units	Years 1	2	3	4	5
				Moderate Efficacy		
Barrows and gilts (liveweight prices)	$/cwt.	2.32	1.62	1.11	.72	.54
Percentage change	Pct.	5.02	3.83	2.34	1.59	1.14
Broilers (RTC wholesale price)[2]	¢/lb.	5.03	2.75	1.77	1.46	1.34
Percentage change	Pct.	12.99	6.94	3.09	2.67	2.25
Turkeys (liveweight farm prices)	¢/lb.	3.39	1.90	1.32	1.19	1.19
Percentage change	Pct.	11.61	6.70	3.42	3.51	3.54
Fed beef (steer price, Omaha)	$/cwt.	1.68	1.33	1.06	.60	0
Percentage change	Pct.	4.30	3.30	2.00	1.00	0
				High Efficacy		
Barrows and gilts (liveweight prices)	$/cwt.	7.45	5.49	3.80	2.37	1.67
Percentage change	Pct.	16.13	12.97	8.00	5.24	3.53
Broilers (RTC wholesale price)[2]	¢/lb.	13.80	7.91	5.15	4.08	3.60
Percentage change	Pct.	35.65	20.00	8.98	7.46	6.04
Turkeys (liveweight farm price)	¢/lb.	7.49	4.66	3.43	2.98	2.98
Percentage change	Pct.	25.64	16.42	8.88	8.79	8.88
Fed beef (steer price, Omaha)	$/cwt.	6.02	4.55	2.65	1.20	.60
Percentage change	Pct.	15.34	11.27	5.03	2.00	.96

[1] Drugs considered banned were penicillin, tetracyclines and sulfa at subtherapeutic levels and nitrofurans at all levels.

[2] RTC = "ready to cook."

From: "Draft Environmental Impact Statement on Subtherapeutic Antibacterial Agents in Animal Feeds,"Bureau of Veterinary Medicine, Food and Drug Administration, July, 1978

TABLE II

Control and Growth Promotion Claims for Penicillin, Tetracyclines, Their Combinations and Available Substitutes.*

DRUG	SPECIES	USE INDICATION	SUBST. DRUG AND DOSE
Penicillin (2.4-50 g/ton)	chickens and turkeys	Growth promotion, feed efficiency.	Arsanilic Acid or Sodium Arsanilate (90 g/ton) Bacitracin (Zn or M.D.)** (4-50 g/ton) Bambermycins (1-2 g/ton) Erythromycin (4.6-18.5 g/ton) Lincomycin (2-4 g/ton) Oleandomycin (1-2 g/ton) Tylosin (4-50 g/ton) Roxarsone (0.0025-0.005%)
Penicillin (50-100 g/ton)	chickens and turkeys	Prevention & treatment of chronic respiratory disease (CRD), blue comb and infectious sinusitis.	Bacitracin (Zn or M.D.) (50-100 g/ton) Erythromycin (CRD only) (92.5 g/ton)
(10-50 g/ton)	swine	Growth promotion, feed efficiency.	Bacitracin (Zn or M.D.) (10-50 g/ton) Carbadox (10-25 g/ton) Erythromycin (9.25-64.75 g/ton) Bambermycins (2 g/ton) Oleandomycin (5-11.25 g/ton) Virginiamycin (10 g/ton) Tylosin (10-100 g/ton)

* Partial Listing

**Zn=Zinc

M.D.= methylene disalicylate

TABLE II (CONTINUED)

DRUG	SPECIES	USE INDICATION	SUB. DRUG AND DOSE
Penicillin (2.4-38 g/ton) plus streptomycin (12-47.6 g/ton)	chickens and turkeys	Growth promotion and feed efficiency.	Arsanilic Acid (90 g/ton) Bacitracin (Zn or M.D.) (4-50 g/ton) Bambermycins (1-2 g/ton) Erythromycin (4.6-18.5 g/ton) Roxarsone (0.0025-0.005%) Tylosin (4-50 g/ton) Oleandomycin (1-2 g/ton) Lincomycin (2-4 g/ton)
90 - 180 g/ton (of the combination)	chickens	Treatment of chronic respiratory disease (air-sac infection), bluecomb (nonspecific infectious enteritis).	Bacitracin (Zn or M.D.) (50-100 g/ton) Erythromycin (CRD only) (92.5 g/ton)
	turkeys	Treatment of infectious sinusitis, blue comb(mud fever), hexamitiasis.	Bacitracin (M.D.) (except hexamitiasis) (100-200 g/ton)
90-270 g/ton (of the combination)	swine	Treatment of bacterial swine enteritis.	Bacitracin (Zn or M.D.) (100 g/ton) Carbadox (50 g/ton) Virginiamycin (100 g/ton then 50 g/ton)

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TABLE II (CONTINUED)

DRUG	SPECIES	USE INDICATION	SUB. DRUG AND DOSE
Chlortetracycline (CTC) (10-50 g/ton)	chicken and turkeys	Growth promotion, feed efficiency.	Arsanilic Acid or Arsanilate Sodium (90 g/ton) Bambermycins (1-2 g/ton) Lincomycin (2-4 g/ton) Oleandomycin (1-2 g/ton) Tylosin (4-50 g/ton) Roxarsone (0.0025-0.005%) Bacitracin (Zn or M.D.) (4-50 g/ton) Erythromycin (4.6-18.5 g/ton)
CTC (100-200 g/ton)	chickens	Treatment of chronic respiratory disease, bluecomb; prevention of synovitis.	Bacitracin (M.D.) (100-200 g/ton) (no substitute for synovitis)
CTC (100-200 g/ton)	turkeys	Treatment of bluecomb, infectious sinusitis, hexamitiasis; prevention synovitis.	Tylosin (800 to 1000 g/ton) Bacitracin (M.D.) (100-200 g/ton) (no substitute for synovitis)
CTC (100-200 g/ton)	swine	Treatment of bacterial swine enteritis.	Bacitracin (M.D.) (100 g/ton)
CTC (10-50 g/ton)	swine	Growth promotion, feed efficiency.	Carbadox (10-25 g/ton) Bambermycins (2 g/ton) Erythromycin (9.25-64.75 g/ton) Bacitracin (M.D. or Zn) (10-50 g/ton) Virginiamycin (10 g/ton)

TABLE II (CONTINUED)

DRUG	SPECIES	USE INDICATION	SUB. DRUG AND DOSE
CTC (continued) (10-50 g/ton)	swine	Growth promotion, feed efficiency.	Oleandomycin (5-11.25 g/ton) Tylosin (10-100 g/ton)
CTC (50-100 g/ton)	swine	Maintenance of weight gain in the presence of atrophic rhinitis; reduction of incidence of cervical abscesses.	Tylosin (100 g/ton) (no substitute for cervical abscesses)
CTC (70 mg/head/day)	cattle	As an aid in the reduction of condemnation of livers due to liver abscesses.	Bacitracin (M.D.) (70 or 250 mg/head/day) Tylosin (8-10 g/ton)
CTC (70 mg/head/day)	cattle	Aid in prevention of foot rot.	Sulfaethoxypyridazine (25 mg/lb bd.wt./day)
CTC (70 mg/head/day)	cattle	Growth promotion and feed efficiency.	Bacitracin (Zn) (35-70 mg/head/day) Monensin (5-30 g/ton)
CTC (0.5 mg/lb bwt/day)	beef cattle over 1500 lb in wt.	Control of active infectious anaplasmosis.	No approved substitute.
CTC (80 mg/head/day)	sheep	Aid in reducing the incidence of vibrionic abortion in breeding sheep.	No approved substitute
Oxytetracycline (OTC) (100-200 g/ton)	chickens	As an aid in the prevention of fowl cholera.	Sulfadimethoxine plus ormetoprim

TABLE II (CONTINUED)

DRUG	SPECIES	USE INDICATIONS	SUB. DRUG AND DOSE
OTC (10-50 g/ton)	chickens	For increased weight gain, improved feed efficiency.	Arsanilic Acid or Arsanilate Sodium (90 g/ton) Bacitracin (M.D. or Zn) (4-50 g/ton) Bambermycins (1-2 g/ton) Erythromycin (4.6-18.5 g/ton) Lincomycin (2-4 g/ton) Oleandomycin (1-2 g/ton) Tylosin (4-50 g/ton) Roxarsone (0.0025-0.005%)
OTC (7.5-50 g/ton)	swine	Growth promotion, feed efficiency.	Bacitracin (Zn or M.D.) (10-50 g/ton) Carbadox (10-25 g/ton) Erythromycin (9.25-64.75 g/ton) Bambermycins (1-2 g/ton) Oleandomycin (5-11.25 g/ton) Virginiamycin (10 g/ton) Tylosin (10-100 g/ton)
OTC (25-75 mg/ head/day)	calves	Growth promotion, feed efficiency.	Bacitracin (Zn) (35-70 mg/head/day)
OTC (50-100 g/ton)	chickens	Prevention of blue comb.	Bacitracin (Zn or M.D.) (50-100 g/ton)
OTC (200 g/ton)	chickens and turkeys	Control of infectious synovitis.	No approved substitute.

TABLE II (CONTINUED)

DRUG	SPECIES	USE INDICATION	SUB.DRUG AND DOSE
OTC (100-200 g/ton)	chickens	Prevention of chronic respiratory disease.	Bacitracin (Zn or M.D.) (50-100 g/ton)
OTC (75-80 mg/head/day)	cattle	As an aid in reduction of the incidence of liver abscesses.	Bacitracin (M.D.) (70 or 250 mg/head/day) Tylosin (8-10 g/ton)
Oxytetracycline (50 g/ton) plus Neomycin base* (35-140 g/ton)	chickens	Prevention of diseases during periods of stress. As an aid in the prevention of bacterial enteritis and in the control of bluecomb (mud fever or non-specific enteritis).	Bacitracin (Zn or M.D.) (50-100 g/ton)
OTC (100-200 g/ton) plus Neomycin base (35-140 g/ton)	chickens	Prevention of complicated chronic respiratory disease (air-sac infection) and control of complicated CRD by lowering mortality and severity during outbreaks. As an aid in the prevention of bacterial enteritis and in the control of bluecomb (mud fever or non-specific enteritis).	Bacitracin (Zn or M.D.) (50-100 g/ton) Tylosin (800-1000 g/ton) Erythromycin (92.5 g/ton)

*Neomycin use levels are expressed as grams of neomycin base per ton (70% neomycin sulfate levels). For example, 140 g neomycin base is equivalent to 200 g neomycin sulfate.

TABLE II (CONTINUED)

DRUG	SPECIES	USE INDICATION	SUB. DRUG AND DOSE
OTC (50 g/ton) plus Neomycin (35-140 g/ton)	swine	As an aid in the prevention of bacterial enteritis, baby pig diarrhea, vibrionic dysentery, bloody dysentery, and salmonellosis.	Bacitracin (M.D.or Zn) (100 g/ton) (enteritis only) Carbadox (50 g/ton) Tylosin (for dysentery) (100 then 40 g/ton) Virginiamycin (100 g/ton for 2 weeks followed by 50 g/ton) (for dysentery)
OTC (100 g/ton) plus Neomycin (70-140 g/ton)	swine	As an aid in the treatment of bacterial enteritis.	Bacitracin (M.D.or Zn) (100 g/ton)
OTC (50-150 g/ton) plus Neomycin base (70-140 g/ton)	swine	Aid in the maintenance of weight gains and feed consumption in the presence of atrophic rhinitis.	Tylosin (100 g/ton)
OTC (100 g/ton) plus Neomycin base (70-140 g/ton)	calves	Aid in the treatment of bacterial enteritis (scours).	No approved substitute.

TABLE II (CONTINUED)

DRUG	SPECIES	USE INDICATION	SUB.DRUG AND DOSE
* CTC (100 g/ton) plus Sulfamethazine (100 g/ton) and Penicillin (from procaine penicillin) (50 g/ton) - or - CTC (100 g/ton) plus Sulfathiazole (100 g/ton) and Penicillin (50 g/ton)	swine	Individual claims For increase in rate of weight gain and improvement of feed efficiency.	See list under penicillin on first page of table.
		For control of swine dysentery (vibrionic dysentery, bloody scours, or hemorrhagic dysentery); control of bacterial swine enteritis (salmonellosis or necrotic enteritis caused by *Salmonella choleraesuis*); increase rate of weight gain and improved feed efficiency.	Carbadox (50 g/ton)
		Prevention of swine dysentery (vibrionic)	Virginiamycin (100 then 50 g/ton) Tylosin (100 then 40 g/ton)
		Maintaining weight gains and feed efficiency in the presence of atrophic rhinitis	Tylosin (100 g/ton)
		Growth promotion and feed efficiency	See list under penicillin on first page of table.
		Aid in the prevention of bacterial swine enteritis (scours)	Bacitracin (Zn or M.D.) (100 g/ton) Carbadox (50 g/ton)

*Abbreviation ASP/CSP

TABLE II (CONTINUED)

DRUG	SPECIES	USE INDICATION	SUB.DRUG AND DOSE
ASP/CSP (continued)	swine	For the treatment of bacterial swine enteritis (scours)	Bacitracin (100 g/ton) Carbadox (50 g/ton)
		For increase in rate of weight gain and improvement of feed efficiency from weaning to 120 lbs (starter and grower feeds only)	Virginiamycin (10 g/ton)
		As an aid in the control of swine dysentery in swine up to 120 lb. For use in animals or on premises with a history of swine dysentery, but where symptoms have not yet occurred.	Virginiamycin (25 g/ton)
		For treatment and control of swine dysentery (bloody scours or hemorrhagic dysentery) up to 120 lbs.	Virginiamycin (100 g/ton then 50 g/ton)
		For treatment of swine dysentery for two weeks in non-breeding swine over 120 lb.	Virginiamycin (100 g/ton)

TABLE II (CONTINUED)

DRUG	SPECIES	USE INDICATIONS	SUB.DRUG AND DOSE
CTC (350 mg/head/ day) plus Sulfamethazine (350 mg/head/ day)	cattle	Aid in the maintenance of weight gain in the presence of respiratory disease such as shipping fever.	No approved substitute.

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Mycotic Diarrhea
  Nystatin 261
Non-Specific Enteritis (see Bluecomb)
Paracolon
  Furazolidone 218
Paratyphoid
  Furazolidone 218
Pullorum
  Furazolidone 218
Quail Disease (Ulcerative Enteritis)
  Furazolidone 218
Roundworms (see Worms)
Stress
  Bacitracin 145
  Bacitracin Methylene Disalicylate 137
  Bacitracin Zinc 146
  Chlortetracycline 186
  Erythromycin 207
  Furazolidone 218
  Oxytetracycline 263
Synovitis
  Chlortetracycline 186
  Furazolidone 218
  Novobiocin 259
  Oxytetracycline 263
Tapeworms (see Worms)
Typhoid, Fowl
  Furazolidone 218
  Sulfaquinoxaline 322
Ulcerative Enteritis (see Quail Disease)
Worms
  Capillary Worms
  Coumaphos 199
  Hygromycin B 226
  Cecal Worms (Heterakis)
  Butynorate, Piperazine and Phenothiazine 182
  Coumaphos 199
  Hygromycin B 226
  Phenothiazine 283
  Large Roundworms (Ascaris)
  Butynorate, Piperazine and Phenothiazine 182
  Hygromycin B 226
  Piperazine 286
  Tapeworms
  Butynorate, Piperazine and Phenothiazine 182

CHINCHILLA

MEDICINAL USES

Fungus Infections
  Griseofulvin 225

DUCKS

NUTRITIONAL USES

Carcass Quality
  Thyroprotein 336
Growth Promotion
  Thyroprotein 336
Stomachic Appetizer
  Nux Vomica Extract 260

MEDICINAL USES

Bacterial Enteritis
  Neomycin 253

FISH

MEDICINAL USES

Hemorrhagic Septicemia
  Oxytetracycline 260
Pseudomonas Disease
  Oxytetracycline 263
Ulcer Disease
  Oxytetracycline 263

GEESE

NUTRITIONAL USES

Stomachic Appetizer
  Nux Vomica Extract 260

GOATS

NUTRITIONAL USES

Fertility and Libido
  Thyroprotein 336
Growth Promotion
  Thyroprotein 336
Milk and Butterfat Stimulator
  Thyroprotein 336

MEDICINAL USES

Bacterial Enteritis
  Neomycin 253
Gastrointestinal Roundworms (see Worms)
Worms
  Gastrointestinal Roundworms
  Thiabendazole 335
  Stomach Worms
  Phenothiazine 283

HORSES AND MULES

NUTRITIONAL USES

Growth Promotion
  Chlortetracycline 186

MEDICINAL USES

Bacterial Enteritis
  Neomycin 253
Strongyle Worms
  Phenothiazine 283

MINK

NUTRITIONAL USES

Growth Promotion
  Chlortetracycline 186
  Oxytetracycline 260
Pelt Promotion
  Chlortetracycline 186
  Oxytetracycline 260

MEDICINAL USES

Bacterial Diarrhea
  Nitrofurazone 257
  Oxytetracycline 260
Bacterial Enteritis
  Bacitracin 145
  Bacitracin Methylene Disalicylate 137
  Bacitracin Zinc 146
  Neomycin 253
Staphylococcic Infection
  Novobiocin 259

PHEASANTS

NUTRITIONAL USES

Growth Promotion
  Bacitracin 145
  Bacitracin Methylene Disalicylate 137
  Bacitracin Zinc 146
  Penicillin 280

QUAIL

NUTRITIONAL USES

  Bacitracin 145
  Bacitracin Methylene Disalicylate 137
  Bacitracin Zinc 146
  Penicillin 280

RABBITS

NUTRITIONAL USES

Growth Promotion
  Oxytetracycline 263

MEDICINAL USES

Coccidiosis
  Sulfaquinoxaline 322

SHEEP

NUTRITIONAL USES

Fertility and Libido
  Thyroprotein 336
Growth Promotion
  Chlortetracycline 186
  Oxytetracycline 263

MEDICINAL USES

Bacterial Diarrhea
  Oxytetracycline 263
Bacterial Enteritis
  Neomycin 253
Bankrupt Worms (see Worms)
Enterotoxemia (Overeating Disease)
  Chlortetracycline 186
  Neomycin 253
  Oxytetracycline 263
Gastrointestinal Roundworms (see Worms)
Hookworms (see Worms)
Lumpy Jaw
  Ethylenediamine Dihydriodide 214
Overeating Disease (see Enterotoxemia)
Scours (see Bacterial Diarrhea)
Stomach Worms (see Worms)
Urinary Calculi (Waterbelly)
  Ammonium Chloride 170
Vibrionic Abortion
  Chlortetracycline 186
Worms
  Gastrointestinal Roundworms
  Thiabendazole 337
  Hookworms
  Phenothiazine 280
  Stomach Worms
  Phenothiazine 283

SWINE

NUTRITIONAL USES

Growth Promotion
- Arsanilic Acid or Sodium Arsanilate 124
- Bacitracin 145
- Bacitracin Methylene Disalicylate 157
- Bacitracin Zinc 166
- Bambermycins 176
- Carbadox 183
- Chlortetracycline 186
- Erythromycin 207
- Oleandomycin 262
- Furazolidone 218
- Oxytetracycline 265
- Penicillin 280
- Roxarsone 295
- Tylosin 327
- Virginiamycin 332

Litter Production Efficiency
- Dichlorvos 203

MEDICINAL USES

Atrophic Rhinitis
- Chlortetracycline 186
- Oxytetracycline 265
- Tylosin 327

Bacterial Swine Enteritis (Scours)
- Bacitracin 145
- Bacitracin Methylene Disalicylate 157
- Bacitracin Zinc 166
- Carbadox 183
- Chlortetracycline 186
- Furazolidone 218
- Neomycin 253
- Nitrofurazone 257
- Oxytetracycline 263
- Virginiamycin 332

Cervical Abscesses
- Chlortetracycline 186

Dysentery
- Arsanilic Acid or Sodium Arsanilate 124
- Carbadox 183
- Lincomycin 235
- Roxarsone 295
- Virginiamycin 332

Dysentery, Vibrionic
- Carbadox 183
- Furazolidone 218
- Neomycin 253
- Oxytetracycline 263
- Tylosin 327

Large Roundworms (see Worms)

Leptospirosis
- Chlortetracycline 186
- Oxytetracycline 260

Mucus
- Ethylenediamine Dihydriodide 214

Necrotic Enteritis
- Carbadox 183
- Chlortetracycline 186
- Furazolidone 218
- Neomycin 253
- Oxytetracycline 263

Nodular Worms (see Worms)

Roundworms (see Worms)

Salmonellosis (see Necrotic Enteritis)

Scours (see Bacterial Swine Enteritis)

Stress
- Chlortetracycline 186

Worms
- Large Roundworms
- Dichlorvos 203
- Hygromycin B 226
- Levamisole Hydrochloride 233
- Piperazine 286
- Pyrantel Tartrate 290
- Thiabendazole 321
- Lungworms
- Levamisole Hydrochloride 233
- Nodular Worms
- Dichlorvos 203
- Hygromycin B 226
- Levamisole Hydrochloride 233
- Phenothiazine 283
- Piperazine 286
- Pyrantel Tartrate 290
- Thick Stomach Worms
- Dichlorvos 203
- Threadworms
- Levamisole Hydrochloride 233
- Whipworms
- Dichlorvos 203
- Hygromycin B 226

TURKEYS

NUTRITIONAL USES

Airsacculitis
- Oxytetracycline 263

Bloom and Feathering
- Arsanilic Acid or Sodium Arsanilate 124

Egg Hatchability
- Bacitracin 145
- Bacitracin Zinc 166
- Oxytetracycline 263

Egg Production
- Bacitracin 145
- Bacitracin Zinc 166
- Oxytetracycline 263

Growth Promotion
- Arsanilic Acid or Sodium Arsanilate 124
- Bacitracin 145
- Bacitracin Methylene Disalicylate 157
- Bacitracin Zinc 166
- Chlortetracycline 186
- Dimetridazole 204
- Erythromycin 207
- Furazolidone 218
- Oleandomycin 262
- Oxytetracycline 263
- Penicillin 280
- Roxarsone 295

Pigmentation
- Arsanilic Acid or Sodium Arsanilate 124

Stomachic Appetizer
- Bacitracin 145
- Nux Vomica Extract 260

MEDICINAL USES

Bacterial Enteritis
- Neomycin 253

Blackhead
- Carbarsone 184
- Dimetridazole 204
- Furazolidone 218
- Ipronidazole 230
- Nitarsone 256

Bluecomb (Non-Specific Enteritis)
- Bacitracin 145
- Bacitracin Methylene Disalicylate 157
- Bacitracin Zinc 166
- Chlortetracycline 186
- Furazolidone 218
- Neomycin 253
- Oxytetracycline 263
- Penicillin 280

Breast Blisters
- Novobiocin 259

Cecal Worms (see Worms)

Cholera, Fowl
- Novobiocin 259
- Sulfadimethoxine and Ormetoprim 318
- Sulfaquinoxaline 322

Chronic Respiratory Disease (CRD)
- Bacitracin 145
- Erythromycin 207
- Penicillin 280

Coccidiosis
- Amprolium 110
- Butynorate 181
- Nitrofurazone 257
- Sulfadimethoxine and Ormetoprim 318
- Sulfaquinoxaline 322
- Zoalene 335

Hepatitis, Infectious
- Furazolidone 218

Heterakis (see Worms, Cecal)

Hexamitiasis
- Butynorate 181
- Chlortetracycline 186
- Furazolidone 218
- Oxytetracycline 263

Histomoniasis (see Blackhead)

Large Roundworms (see Worms)

Leucocytozoonosis
- Clopidol 196

Mucus
- Ethylenediamine Dihydriodide 214

Mud Fever (see Bluecomb)

Mycosis, Crop
- Nystatin 261

Mycotic Diarrhea
- Nystatin 261

Non-Specific Enteritis (see Bluecomb)

Paracolon
- Furazolidone 218

Paratyphoid
- Furazolidone 218

Pullorum
- Furazolidone 218

Quail Disease
- Furazolidone 218

Roundworm (see Worms)

Secondary Bacterial Invasions
- Nitrofurazone 257

Sinusitis, Infectious
- Bacitracin 145
- Bacitracin Methylene Disalicylate 157
- Bacitracin Zinc 166
- Chlortetracycline 186
- Oxytetracycline 263

Stress
- Bacitracin 145
- Bacitracin Methylene Disalicylate 157
- Chlortetracycline 186
- Erythromycin 207
- Furazolidone 218
- Oxytetracycline 263

Synovitis
- Chlortetracycline 186
- Furazolidone 218
- Novobiocin 259
- Oxytetracycline 263

Ulcerative Enteritis (see Quail Disease

Worms
- Cecal Worms (Heterakis)
- Phenothiazine 283
- Piperazine 286
- Large Roundworms
- Piperazine 286
- Tapeworms
- Butynorate, Piperazine and Phenothiazine 181

Feed Additives: A Crutch for Poor Management?

Have hogs reached a point similar to poultry where good management, nutrition, animal health practices and sanitation have negated feed additive responses in terms of growth and feed efficiency? Are antibiotics in general used unnecessarily and only as a crutch for poor management? Yes, according to the presentations on this page and page 41. Jim Green addresses the possibility of hog compensation for feed additive deprivation, while Drs. J.J. Shull and B.P. Cardon look at the misuse of antibiotics in treating calf scours.

By Dr. Jim Green
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For more than 25 years, starting, growing, developing and finishing pigs have been responding with increased gains and improved feed efficiency upon consuming feeds containing feed additives.

However, feed management and animal health practices have improved in recent years via isolation of new breeding stock, timely vaccinations, proper nutrition, control of internal and external parasites and improved waste disposal and sanitation. With these improvements have come numerous failures of feed additives to promote better gains and feed conversion especially for finishing pigs. Sometimes advantages from earlier feeding of antibiotics completely disappear during the latter phases of developing-finishing.

Should starting or growing pigs be looked upon as underprivileged if they have been deprived of feed additives in their rations? The pig has an incredible ability to compensate, on an adequate ration, in a later phase in spite of inadequate nutrition in an earlier phase. Is it possible, then, that with top management and nutrition pigs are able to "tough it out" in the absence of feed additives and can be just as healthy and perhaps more profitable by a similar compensation?

At various times in the last 6-7 years, tests have been conducted with feed additives at the Research Farm, Marshall. The farm still has the usual problems of various types of scours, SMEDI among the sows, a touch of bloody scours and eperythrozoonosis among the breeding and replacement animals despite its newness. These facilities are not sterile or well isolated. Feeder pigs are brought onto the farm into nearby facilities and cared for by many of the same swine management personnel that care for the animals used in research trials. Therefore, feed additives should have as great an effect at these facilities as at well-managed commercial facilities.

Data summarized in Tables 1 and 2 indicate the gain and feed conversion response obtained at this farm when feed additives were used in the rations of weaning pigs. Further, Table 2 indicates a sustained response in gain when an additive combination was continued on to about 75 lb. These responses are in line with much of the published data on feed additives, i.e., the strong response by younger pigs.

The trial summarized in Table 3 was conducted to test a number of the so-called "high level" combinations and singular additives for growing pigs (to 75 lb.), followed by appropriate lower level additives to about 120 lb. and none from 120 lb. to market. Four of five additives or combinations gave a highly significant ($P < 0.01$) response over the control ration on gain and two gave a significant ($P < 0.05$) response on feed conversion up to 75 lb. However, between 75 and 120 lb. weight, the only significant difference in gain occurred between two "lower level" additives and only one additive stim-

EDITOR'S NOTE: Dr. Jim Green is director of nutrition in the research and nutrition, quality control section of MFA, Columbia, Mo.

TABLE 1. Feed Additives for Weaning Pigs (19% Pelleted Commercial Pig Starter, Fall 1974)

	Carbadox 50 g/ton	Virginiamycin 25 g/ton	Non-Medicated Control
Daily gain (lb.)	1.22^{a}	1.20^{a,b}	1.08^{b}
Feed/gain	1.83^{c,d}	1.79^{c}	1.97^{d}
Final weight (lb.)	55.6	56.0	54.0

Each treatment mean represents five replications of 15-17 pigs per lot with average initial weight of 23 lb.

a,b. Means with different superscripts are significantly different ($P < 0.01$).

c, d. Means with different superscripts are significantly different ($P < 0.05$).

TABLE 2. Feed Additive Combination for Weaning and Growing Pigs (19% Protein Corn-Soy Meal Ration, Fall 1973)

	Oxytetracycline 100 g Furazolidone 100 g Arsanilic Acid 90 g	Non-Medicated Control Ration
Weaning to 50 lb.		
Daily gain (lb.)	1.04	0.92
Feed/gain	2.00	2.00
Weaning to 75 lb.		
Daily gain (lb.)	1.24	1.10
Feed/gain	2.33	2.34
Final weight	79.2	74.5

Each treatment mean represents six replications of 15-16 pigs per lot or a total of 104 pigs per treatment with an initial weight of 23 lb.

a,b. Means are significantly different ($P < 0.01$).

TABLE 4. Bloody Scours Preventives for Developing-Finishing Pigs (14% Protein Pelleted Ration, Winter 1976-77)

		Virginiamycin 25 g/ton	Lincomycin
Medication to 120 lb.	None	Bacitracin MD-	40 g/ton
Medication 120 lb. to Market	None	Roxarsone 30/50 g/ton	40 g/ton
To 120 lb.			
Daily gain (lb.)	1.62^{a}	1.68^{a,b}	1.70^{b}
Feed/gain	3.15^{c}	3.02^{c,d}	3.02^{d}
Feed cost/cwt. gain ($)^{e}	24.73	24.70	23.77
Margin above feed cost for period ($/Pig)^{1}	4.79	5.60	5.79
120 lb. to Market			
Daily gain (lb.)	1.77	1.78	1.74
Feed/gain	3.65	3.60	3.60
60 lb. to Market			
Daily gain (lb.)	1.71	1.73	1.76
Feed/gain	3.40	3.30	3.30
Final weight (lb.)	213.9	215.1	216.2
Feed cost/cwt. gain ($)^{e}	28.30	26.90	26.60
Margin above feed cost for test ($/Pig)^{1}	6.91	6.84	7.81

Each treatment mean represents eight replications of 10 pigs per lot of 60 lb. initial weight.

a,b. Means with different superscripts are significantly different ($P < 0.05$).

c,d. Means with different superscripts are significantly different ($P < 0.05$).

e. Non-medicated pellets about $7.60; with Virginiamycin, about $9.20; with Lincomycin, about $8.40, and with Bacitracin MD-Roxarsone about $8.50 per cwt.

1. Based on $35 live hog market and feed costs above.

TABLE 3. Feed Additives for Growing Developing Pigs — None for Finishing, Spring 1978 (18-14-12% Protein Sequence of Corn-Soy Meal Rations)

Medication to 75 lb. (g/ton)	Chlortetracycline Sulfamethazine Penicillin 100/100/50	Tylosin Sulfamethazine 100/100	Oxytetracycline Furazolidone Arsanilic Acid 100/100/90	Carbadox 50	Virginiamycin 25	None
Daily gain (lb.)	1.31^{a}	1.18	1.28^{a}	1.29^{a}	1.20^{a}	1.05^{b}
Feed/gain	2.40	2.60	2.37^{c}	2.39^{c}	2.40	2.61^{d}
Subsequent Medication to 120 lb. (g/ton)	Bacitracin MD- Roxarsone 30/50	Tylosin 20	Oxytetracycline 20	Chlortetracycline 10	Virginiamycin 10	None
Daily gain (lb.)	1.57^{e}	1.59^{e}	1.52^{f}	1.57^{e}	1.59^{e}	1.50^{g}
Feed/gain	2.86	2.79	2.91^{1}	2.89^{1}	2.87^{1}	2.90
No Medication 120 lb. to Market						
Performance, Entire Trial						
Daily gain (lb.)	1.52	1.49	1.48	1.51	1.53	1.50
Feed/gain	3.20	3.16	3.09	3.15	3.23	3.17
Final weight (lb.)	213.3	215.6	222.4	211.8	216.4	213.1

Each treatment mean represents four replications of nine or ten pigs per lot.

a,b,e,f,g. Means with different superscripts are significantly different ($P < 0.01$).

c,d. Means with different superscripts are significantly different ($P < 0.05$).

1. Means do not differ significantly ($P < 0.05$)

TABLE 5. Medication in Developing-Finishing Rations (g/Ton in 14% Pelleted Rations, Fall 1978)

	Bacitracin MD	Bacitracin-Zn	Tylosin	Bambermycins	Chlortetracycline	None
75 to 120 lb.	50	40	40	4	50	0
120 lb. to Market	30	20	20	2	50	0
Daily gain (lb.)	1.80	1.79	1.76	1.83	1.71	1.76
Feed/gain	3.37	3.36	3.30	3.45	3.31	3.35
Final weight (lb.)	217.5	216.6	224.5	211.8	219.0	216.3

Each treatment mean represents four replications of 10 pigs per lot with average initial weight of 70 lb.

ained better ($P < 0.01$) feed conversion than the control ration. Between 120 lb. and market weight, when all pigs were fed non-medicated rations, any pigs which were previously behind outperformed such that the daily gain and feed conversion for the entire trial were not significantly different ($P < 0.05$). If economics were applied to this trial, pigs fed non-medicated rations would be the most profitable. Does this data say feed additive responses are temporary in well-managed pigs?

Table 4 shows data from feeding two bloody scours preventives from 80 to 120 lb., and one of them on to market weights. The other, for Food & Drug Administration compliance, was replaced with a combination with claims for growth promotion and feed conversion from 120 lb. to market weight. While it was numerically or statistically ($P < 0.05$) and economically advantageous to feed the additives to 120 lb., the statistical and economic advantages had disappeared when the pigs reached market weight. Other than possible protection from bloody scours, there was no net effect from these additives.

Table 5 summarizes another trial which tested five different feed additives fed from 75 lb. to market weight. One of these (Bacitracin-Zn) had a reduction in level at 125 lb. while all others were fed at the same rate for the entire trial. Only one of these additives, tylosin, gave any hint of a growth promotion effect, and that was only numerical. Note the best numerical feed conversion was actually with the non-medicated ration. Do we need feed additives for growth and feed conversion promotion in well-managed developing-finishing hogs?

TABLE 6. Medication in Finisher Rations (g/Ton 14% Pelleted Ration, Spring 1979)

	Bacitracin MD	Virginiamycin	Non-Medicated
	20	10	
Daily gain (lb.)	1.78	1.78	1.77
Feed/gain	2.97	2.94	2.95
Final weight (lb.)	219.3	219.8	218.7

Each treatment mean represents four replications of 10 pigs per treatment with average initial weight of 102 lb.

The data in Table 6 show no advantage for two antibiotics fed from 102 lb. to market weight. Note the performance of pigs summarized in Tables 4, 5 and 6 are all very good in contrast to rather mediocre performance of those shown in Table 3, yet all show the same trend.

All these data show no significant growth, feed conversion or economic advantage by using feed additives for finishing hogs. Are we reaching a point similar to the poultry industry, where, because of good management, nutrition, animal health practices and sanitation, we cannot expect feed additive responses in terms of growth and feed efficiency for finishing hogs? I am of the opinion that the answer is "yes."

On visiting swine production facilities and discussing such visits and reviewing slides of visits by co-workers, we are convinced much of the use of feed additives in finishing hogs is a substitute for proper management and animal health practices. I'm equally convinced the levels of most additives used in these cases, short of being totally illegal, aren't high enough to offset the shortcomings of management and animal health practices.

Perhaps the data presented here would be different if all the pigs had been purchased via feeder pig auctions, etc. But for the farrow to finish operation, these data even shed some doubt on the duration of responses seen in starting pigs due to feed additives.

I realize this data is in contrast to much of that presented to protect our continued use of feed additives in all ages of hogs. And, I've often questioned whether the interspersing of control lots among lots receiving feed additives didn't afford a degree of "protection" by location and actually mask the real effect of no additives. However, I'm sure the pure statistician would pull his hair out should we suggest all controls be fed in a single block of lots in the facility.

It appears the need for good "field data" will become even greater to justify the use of additives in finishing hogs. Can we get good data from operations which apparently benefit most from feed additives because of poor management? Perhaps the feed industry and university researchers need to depart from their own facilities to get supporting data on additives for finishing hogs or conclude they are not justified. ◆

The Antibiotic Issue: A Reappraisal Needed

By Drs. J.J. Shull and B.P. Cardon
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Since its introduction in the early 1950s, the practice of feeding antibiotics for disease prevention and growth promotion has become ingrained in American livestock production. The data which justified their use were substantial and, in many cases, their practical application has shown significant economic benefit.

However, in the years since the first use of antibiotics, mutation and selection within bacterial populations have resulted in a marked increase in their resistance to antibiotics, throwing open to question the validity of current application of the early work which was conducted in an environment of susceptible microorganisms.

There has been much concern over the prevention and treatment of calf scours. When antibiotics were first introduced, calf scours was largely a mystery disease. *Salmonella* was recognized as the cause of some severe cases of calf scours, and *Escherichia coli* was suspected in other cases. But nothing was known of the mechanism by which they caused diarrhea, or the role of the normal intestinal flora in preventing it. Virus involvement had not yet been discovered, and fluid therapy had not been developed. The disease was accompanied by high mortality, and antibiotics were the first truly effective tool in dealing with the disease.

E. Coli is now known as the principal cause of infectious diarrhea in calves less than four days old. Many studies over the past several years have illustrated the growth in resistance of *E. coli* isolated from diarrheic calves and pigs to the antibiotics commonly used in the U.S. to prevent and treat calf scours (Table 1). Thus, in the U.S., enteropathogenic *E. coli* is generally resistant to ampicillin, neomycin, streptomycin and the tetracyclines, with neomycin and the tetracyclines the most commonly used antibiotics in milk replacers and scours treatment preparations.

Milk containing prophylactic quantities of neomycin was therefore compared with milk without antibiotic as feed for day-old Holstein calves in a trial at a commercial calf ranch in southern California. Feeding neomycin to calves almost tripled the incidence of scours during the first three days of life (Table 2). In addition, although oral treatment with other antibiotics appeared in most of these cases to control the episodes of scours, the incidence of cases of recurrent diarrhea was five-fold greater when oral antibiotics were employed for therapy than when they were not.

The antibiotics employed have a broad spectrum of activity, meaning they have the ability to inhibit or kill a wide variety of species of bacteria. Therefore, when fed to calves at subtherapeutic levels they destroy a portion of the normal protective bacterial population, but leave the resistant pathogens unaffected. As a result, subtherapeutic levels of antibiotics in feed may favor the development of pathogenic bacteria in the intestinal tract resistant to the antibiotic used and increase the incidence of disease.

But resistance of bacteria to antibiotics is not absolute, and large doses of antibiotics will kill or inhibit a portion of a population of resistant bacteria. Therefore, antibiotic therapy may appear to be effective even when treating scours caused by bacteria resistant to the antibiotic used. Apparently the population of the pathogen is reduced below that necessary to cause disease symptoms, and diarrhea stops.

However, when therapy is discontinued, surviving pathogens face little interference from the depleted normal population, repopulate the intestinal tract and cause a second episode of the disease. To the calf raiser, it appears the treatment worked, and he dismisses the animal suffering the second and third case of scours as a "poor doer," not realizing the treatment method has predisposed the calf to recurrence of the disease.

This is particularly unfortunate because research

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TABLE 1. Percentage of Isolates of Enteropathogenic *E. coli* Sensitive to Antibiotics

Antibiotic	S. Cal.[1]	N.Y.[2]	Pa.[3]	Wis.[4]	Ariz.[3]	[illegible][5]	[illegible]
Ampicillin	0	[illegible]	[illegible]	—	[illegible]	[illegible]	0
Chloramphenicol	47	75	[illegible]	—	[illegible]	70	[illegible]
Furacin	10	—	—	100	—	[illegible]	—
Nitrofurantoin	—	[illegible]	[illegible]	—	[illegible]	—	[illegible]
Gentamicin	[illegible]	97	100	—	[illegible]	—	—
Neomycin	0	13	[illegible]	0	[illegible]	73	77
Streptomycin	0	2	—	0	[illegible]	4	[illegible]
Sulfa	—	[illegible]	[illegible]	—	[illegible]	—	—
Tetracyclines	0	5	27	0	[illegible]	10	[illegible]

1. Shull and Frederick (1978).
2. [illegible] et al. (1979).
3. Shull, unpublished data.
4. [illegible] and [illegible] (1979).
5. [illegible] et al. (1978).

TABLE 2. Incidence and Recurrence of Calf Scours Within Three Days of Birth

	Oral Antibiotic[a]	No Oral Antibiotic[b]
No. of Calves observed	230	174
1st diarrheal episodes (% of population)	46 (20.0)	14 (8.1)
1st repeat diarrheal episodes (% of first episodes)	17 (36.4)	1 (7.1)
Death loss (% of population)	6 (2.6)	2 (1.2)

a. 250 mg neomycin per feeding from birth and treatment per scours with [illegible], spectinomycin and/or sulfa boluses.
b. Gentamicin injectable for persistent cases of scours only.
From: Shull and Frederick (1978).

since 1960 has shown scours is usually a self-limiting disease which will subside spontaneously if the calf is supported by feeding electrolyte solutions to counteract dehydration. In those cases in which the infection progresses beyond the intestinal tract into the tissues and bloodstream, injectable antibiotics are effective. In our study, this approach was equally effective in saving scouring calves; the experience of Roskova (1976) shows it can be superior.

Observations of farm practices have shown well-intentioned misuse of antibiotics is a major problem in both prevention and treatment of calf scours. The livestock manager is not at fault. He's been taught oral antibiotics are safe and effective. But everyone else in the chain from research through drug approval to sale of finished feed and drugs, including consulting nutritionists and veterinarians, has a role to play in the proper instruction of the consumer in use of antibiotic products. The feed industry has not updated the message with the changing environment, and the producer, not really trained in the complexities of physiology and microbiology, misinterprets and gets accused of using antibiotics as a crutch to prop up poor management.

Feed manufacturers feel responsible for misconceptions in livestock management resulting from use of their products if they fail to keep up with technological change and fail to make sure the producer understands how to use the tools provided to him. Feed manufacturers insist on sound data supporting each use of a product and good instructional materials that leave little room for misunderstanding.

Assuming our results in California have wider application, the reeducation process facing the feed industry in calf scours management is awesome. It's almost impossible to find an antibiotic-free milk replacer in the retail feed store because the consumer has been convinced he can't get along without the antibiotic. The calf raiser demands antibiotics in oral preparations available over-the-counter, not knowing these antibiotics available to him are relatively ineffective, and that appropriate electrolyte solutions will serve effectively in most cases. He has been indoctrinated thoroughly, unfortunately for an environmental situation that no longer exists.

How much of this story translates to other uses of antibiotics in the feed industry? In our cattle and swine operations in Arizona, we use antibiotics in feeds only for control of disease outbreaks, not for prevention or growth promotion, because the best performance is obtained that way. Antibiotics are used to control disease outbreaks where appropriate. They may be put in the feed because it's convenient, recognizing the potential hazard to the delicate balance of intestinal microorganisms. Disease situations change from place to place, but one thing is clear: the need for antibiotics in feed is not universal. Each application must be judged on its own merits on the basis of need, efficacy, safety and economics.

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Mr. **Waxman**. Mr. Dingell, I want to commend you for your statement, and Mr. Fortuna for the work he has done in producing this statement. I think it is a thorough and complete call to us from a public health perspective to do something before we are faced with the consequences of what appears to be a looming public health dilemma in a very few short years.

I appreciate the work you have done in producing this statement and this legislation. I think it is one that deserves the scrutiny of the Congress. If what you say, that there are alternatives, and that there is this public health danger, if what you say is in fact the case, then it seems to me the Congress really has no other choice but to act in a very responsible way, and to deal with what is now completely unregulated use of antibiotics in feed. I want to thank you very much.

I would like to recognize Dr. Carter for any questions he may have.

Mr. **Carter**. I thank the distinguished chairman.

You mentioned something that is very meaningful, actually, that is, the overuse of penicillin and tetracycline. Over the years they have been prescribed perhaps too much by physicians, and there is a resistant bacteria developed in the human, and we knew of this long before tetracyclines or penicillins were given to animals.

We saw that resistance develop many years ago. It may well be that this presents a possibility of a terrible strain of bacteria resistant to any antibiotic. That may be so, but it also may be so that we may develop it ourselves, by too frequent prescriptions of this, by humans taking it, because we noted it long before it was fed into animals that certain bacteria were resistant to penicillins and to tetracyclines.

By the way, what is the most dangerous antibiotic that a human can take at the present time?

Mr. **Dingell**. Doctor, I am not prepared to tell you. I would be disposed to say you would be my expert on that matter.

Mr. **Carter**. I thought you were an expert in this field.

Mr. **Dingell**. Mr. Rick Fortuna, who is of my staff, informs me that danger or toxicity depends upon a number of factors: dose, duration, age route, and host factors to name a few, but in general gentamycin is the antibiotic whose current use patterns and toxicity dictate extreme caution.

Mr. **Carter**. I think penicillin is perhaps the most dangerous because it causes more allergic reactions and more deaths than any other. I have seen people after an injection have an attack of angioneurotic edema or faint. For that reason, most physicians keep adrenalin handy, so that they can give that to a patient who has received penicillin.

Another thing. You spoke of salmonella and tetracyclines being the treatment of choice. I rather doubt that in many cases. Perhaps your adviser could tell you. You are running into a very deep subject here.

Mr. **Fortuna**. At one time it was a rare instance to find ampicillin resistant salmonella. In fact, until the recent emergence of ampicillin resistant strains of salmonella, it has displaced chloramphenicol as the drug of choice. That was 1967.

Mr. **Carter**. The most effective drug is chloramphenicol.

Mr. **Fortuna**. That is a primary regimen, but ampicillin has also been widely used in the treatment of salmonella infection.

Mr. **Carter**. It is most seriously resistant to infections. Thank you, Mr. Chairman.

Mr. **Dingell**. Doctor, let me just observe, I am never one to cross swords with you on a medical matter.

Mr. **Carter**. Yes, sir.

Mr. **Dingell**. And I am not one to quarrel that both patients and the medical profession here and abroad throughout the world have not been as prudent and as wise in their use of these powerful antibiotics.

Mr. **Carter**. Yes, sir.

Mr. **Dingell**. Nor am I prepared to tell you that this lack of wisdom in the use of these powerful antibiotics has been a singularly large contributory factor to the situation about which we complain today. And I don't want you to feel that I don't feel that you are as concerned about this problem as am I, because your record is certainly to the contrary.

However, I only submit to you what is the best information I can give you, and the lengthy studies which have been made by a lot of responsible and knowledgeable researchers who have without exception contributed to the wisdom of science on this matter, and who have without exception expressed great concern about the use of human antibiotics in animal feeds.

First of all, two wrongs don't make a right and two mistakes aren't going to help you more than one. What I am really saying is there are other antibiotics which can be used, with greater specificity to attack the particular problems as opposed to widespread use of penicillin and tetracycline in animal feeds, and it is for controls in that particular regard that I appear before this committee to make the plea that I make today.

Mr. **Carter**. I want to commend you on your work. It is very good, I think.

By the way, you mentioned Dr. Van Leeuwen. Did you mean Dr. Anthony Van Leeuwenhoek?

Mr. **Dingell**. No, sir.

Mr. **Carter**. I wouldn't think so. He died 400 years ago. Thank you.

Mr. **Waxman**. Thank you, Dr. Carter. Mr. Dannemeyer.

Mr. **Dannemeyer**. I am curious about something, Mr. Dingell. I listened to your testimony, I think carefully, and got the impression you questioned the use of penicillin and tetracycline in animal feed. You mentioned that several times. If that is your position, I am curious about something from a conceptual standpoint. Why aren't we suggesting in legislation that the Congress itself bite the bullet and say from a policy standpoint we don't think penicillin and tetracycline should be used in animal feeds any longer, period?

Why are we telling the FDA that it shall, by regulation, designate which drugs may not be used in subtherapeutic doses in animal feed? Why don't we shift the burden from the FDA to Congress to bite this bullet?

If we are convinced it is correct ourselves, why don't we, the Congress, bite the bullet and say to the animal industry of this country, that, hereafter on the basis of our findings, you are not going to be able to use this in animal feed any more, because we feel such action is necessary to protect the public?

Mr. **Dingell.** If you will observe, the bill is really in two parts. Section 2 is the findings. The Congress makes a series of findings that those antibiotics, particularly penicillins and tetracyclines, which are the drugs of choice for use in humans against numerous infectious diseases, are also the primary antibiotics for use in animal feeds in subtherapeutic amounts.

We go on to say:

> The continuous use of these and other antibiotics in subtherapeutic amounts has resulted in the development of pathogenic bacteria in these animals which are singularly and multiply resistant to such antibiotics.

Then we go on and make a number of other findings. Now, the operative section is section 3.

Mr. **Dannemeyer.** I think I understand that.

Mr. **Dingell.** What we do is then we designate that the Secretary shall act by regulation to designate antibiotic drugs which may not be used in subtherapeutic doses in animal feed or ingredients in animal feed. "The Secretary may authorize the use of such antibiotic drug designated under this section in animal feed or ingredients of an animal feed if the Secretary determines its use is required to meet a compelling need."

What I am trying to do here is to craft a flexible tool as opposed to simply come forward with a flat-out prohibition, because I recognize that there may be very good reasons for the use of these in a rather careful fashion. My problem is that I don't think that we ought to just fill our chickens, fill our cattle, fill our hogs, fill our other domestic animals, with feeds containing powerful antibiotics without a cogent and good reason, and to see to it that we get rational rules which are promulgated, which will afford the industry an opportunity to come forward, and make a case as to where and how the rules should be crafted.

In other words, I am saying that with all the work that the Congress has got to do, that this is something that probably under careful and proper guidelines should be vested in the Food and Drug as opposed to simply coming down on the idea and saying that we aren't going to make any of these available in the feeds.

Mr. **Dannemeyer.** Maybe this is too much of a philosophical question for this beautiful morning, but you see, legislating in this fashion creates a situation where people who are opposed to this kind of thing protests against the excess of regulation in our society, by beating on the regulators, in this instance the FDA, but Congress granted them the authority. If we are going to have a problem, Congress is creating it, so why don't we face up to it and take the heat ourselves rather than shifting it to the bureaucrats? I guess that is the question.

Mr. **Dingell.** First of all, I think that the people involved in this thing ought to have a hearing.

Mr. **Dannemeyer.** Here we are.

Mr. **Dingell.** And we ought to craft a rather sensible response, and one which affords a greater recognition of the real world. I am here to urge not a total ban. I am here to point out the concerns that I have about careless use of these very powerful agents, and I am here also to say that a very wide and careful and a selective use of these or of antibiotics or possibly in certain instances a prohibition is wise.

I am here to say that we have the administrative rulemaking procedure is the appropriate mechanism for coping with the intricate and sensitive issue before us. If worse comes to worse, and I become convinced that there is no hope for getting that kind of relief, I may take the course of just simply banning it. I am not here to tell you that a total ban is good. I am here to tell you to the contrary, however, that some more careful controls than are laid in place with regard to these matters are very much in the broad public interest.

Mr. **Dannemeyer.** Thank you.

Mr. **Waxman.** Let me thank you very much for your being with us and for introducing this subject for our consideration. We are now being called to the House floor to vote on two matters that will follow one after another. We will recess now for such time as it will take for us to vote on those matters and return and continue our hearing. Thank you.

[Brief recess.]

Mr. **Waxman.** The meeting will come back to order. It is now my pleasure to recognize our distinguished colleague, Hon. Charles Rose. Many of us know him for his activities in the area of computer technologies which brought to my mind that if you were to present to us a computer printout it would probably be the size of a coin with all that information wrapped up in it. We welcome you to the committee. I know your work on the Agriculture Committee has dealt extensively with this issue, and we are interested in hearing your views, observations and conclusions from your sensitive work in this area.

STATEMENT OF HON. CHARLES ROSE, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NORTH CAROLINA

Mr. **Rose.** Mr. Chairman, I greatly appreciate the opportunity to testify before this most prestigious and important subcommittee of the House about what I consider to be a very sensitive and very important issue. I come here not only as your friend and colleague, but as the chairman of the House Agriculture Subcommittee on Livestock and Grains before I had that subcommittee, I served as chairman of the Subcommittee on Dairy and Poultry of the full Committee on Agriculture, and during that chairmanship I had occasion to conduct a series of hearings on the effect of chemical agents and the regulation thereof on the dairy and poultry industry.

We had a great number of witnesses, including the then Commissioner of the Food and Drug Administration, Mr. Donald Kennedy, who testified precisely on the subject of the effects on human health of subtherapeutic use of antimicrobials in animal feeds. Dr. Kennedy told us that there was absolutely no evidence, that the subtherapeutic usages of antibiotics in animal feed had ever created resistant pathogens harmful to humans; however, there was a theoretical possibility that such could occur, and that as the Commissioner of FDA, he had a moral responsiblity to guard against theoretical possibilities.

Mr. Chairman and members of the committee, I challenge that that is not his responsibility. It may well be the responsibility of this committee and the Congress to look carefully at this subject that has come to be very controversial, but I sincerely urge to you that the findings as listed in H.R. 7285 are simply not so.

I submit that on page 2 of the bill, line 3, it states:

> (2) The continuous use of these and other antibiotics in subtherapeutic amounts has resulted in the development of pathogenic bacteria in animals that are singly and multiply resistant to such antibiotics;
>
> (3) Such pathogenic bacteria are then transmitted to humans where they colonize and cause diseases (such as meningitis, gonorrhea, and salmonellosis) for which there is virtually no effective antibiotic treatment * * *

While in some limited sense the first statement may be correct, I stand on the statement of Dr. Kennedy. The fourth statement on page 2 about the Office of Technology Assessment—I was greatly concerned when OTA issued that rather brief finding, stated so at the time, asked that it be clarified, and here it appears as a part of the preamble or the known truth reported in this legislation.

Mr. Chairman, the possibility that human health may be jeopardized because of this particular livestock management practice of the subtherapeutic feeding does disturb me. Yet, I request that this subcommittee proceed with greater caution on legislation which is clearly a reaction to theoretical risks, not clear and present dangers.

In our Subcommittee of Dairy and Poultry, in addition to Dr. Kennedy we had people from the University of California at Berkeley and others who had been instrumental in the development of tetracycline. They testified that when they first began to practice feeding tetracycline in subtherapeutic quantities to animals, that they expected a resistance to occur that would decrease its effectiveness so that the dosages would have to be constantly increased. They reported to me and to the committee, and it is part of our record, that, to their surprise, this did not occur. Now, it is widely known that the subtherapeutic feeding of tetracycline in the poultry industry produces a cleaner animal, an animal whose gullet, whose total digestive system, is disease free, and is thereby able to convert grain into meat at a substantially higher, rate of efficiency than can a diseased or a partly diseased animal.

Now, there are studies that have been produced, Chase Econometrics Associates is one of them, and I quote from them in my testimony, which points out the increase in cost that the banning of antibiotics in animal feed would cause to the meat industry, which they in turn would be required to pass on to the consumer.

Chase Econometrics Associates estimate a rise in the Consumer Price Index for food of 1.3 to 3.7 percent during the initial year of the ban. This increase would be a direct result of a 5- to 10-percent decrease in broiler production, not because chicken producers weren't trying to produce broilers but because the morbidity and disease the rates would be higher, the animal would simply not be converting grain to meat as efficiently as they now do.

Also, 3.8 percent decrease in turkey production and 1.1 percent decrease in pork production would result.

I would ask, Mr. Chairman, rather than to read my whole testimony, that I be allowed to submit it for the record and make a few other comments, if that is permissible. [See p. 312.]

Mr. **Waxman**. Without objection, the testimony will be included.

Mr. **Rose**. As chairman, as you noted, of the policy group on computers, I like to see long printouts. There is a feeling among the population generally that anything in a printout from a computer is factual and true. I am sure that all of Mr. Dingell's references are correct, but I challenge the statement that all of these printouts of documents prove that there is overwhelming justification for the passage of H.R. 7285.

I would point out that the agricultural appropriations bill of 1980 appropriated $1.5 million for research to generate new information by comparing the health of humans with extensive exposure to animals and/or their products receiving antibiotics at the subtherapeutic level with the health of comparable individuals not so exposed, and the result is the study funded through the National Academy of Sciences by the Congress of the United States. I would like to just quote, if I might, a few words from a National Academy of Sciences study, "The Effects on Human Health of the Subtherapeutic Use of Antimicrobials in Animal Feeds," Mr. Chairman.

The conclusion reached was that there is not enough evidence that antibiotic subtherapeutic feedings have been harmful to humans.

> The committee recommends further research on mechanisms by which subtherapeutic levels of antimicrobials promote growth of animals. Understanding of this mechanism may lead to the development of other substances or procedures, i.e., immunizations that provide the same effect, thereby rendering moot the question of possible effects on human health. However, the committee also recommends continued monitoring and occasional review of the possible effect on humans resulting from the subtherapeutic use of antimicrobials in animal feed.

And the list of those who served on the committee, the National Academy's committee, is impressive. The chairman from the University of Texas School of Public Health in Houston. I see that you have a witness here today from the Harvard Medical School and the Peter Bent Brigham Hospital in Boston, Edward Cass, of the Channing Laboratory at that medical school and hospital, was a member of this panel. There were distinguished academicians on that stuidy group. There were consultants from the University of Missouri, Massachusetts General, Rutgers, Yale, Bolling Air Force Base, University of Illinois, Cornell University, along with the advisory panel on antibiotics and animal feeds from the Board on Agriculture and Renewable Resources, from the Commission on Natural Resources. The cochairmen were from the Virginia Polytechnic Institute and the New York State College of Veterinary Medicine.

I will cease a further reading of the names, but the point is this: No anadromous strain has been created that has overtaken America or hurt one single soul that we can tell from the eating of meat that has been in some way produced through a process that involved the subtherapeutic feedings of antibiotics. There are studies about the handlers of animals that were fed subtherapeutic levels of antibiotics, and in them there has been some increases in resistance to *e. coli* and certain other organisms, but nothing that has been transferred to the population generally.

I would urge the subcommittee to pay careful attention to the National Academy of Sciences study, to not reach a hasty conclusion until all the evidence is in. To do what this subcommittee usually does in the face of a very controversial question such as this, to proceed very cautiously.

I would be happy to join in working with this committee to see that the Congress is fully aware of the recommendations of the National Academy of Sciences, that more study in this area is needed to understand more about these mechanisms. I would sponsor legislation and help expedite its passage in the House Agriculture Committee to get the funding, to better understand the mechanisms of transference that clearly we don't understand today, but to rush out and to ban what has become a basic part of the meat industry's effort to convert grain more efficiently into meat I say is unwise, and I am sure that this committee will not make any unwise decisions.

I appreciate sincerely being allowed to come and testify. Thank you.

Mr. **Waxman**. Without objection, the study entitled, "Economic Impact Study: Effects of a Prohibition on the Use of Selected Animal Drugs" mentioned by Congressman Rose, will be printed as an appendix to the hearing. [See p. 581.]

[Mr. Rose's prepared statement follows:]

Statement of the

Honorable Charles Rose

I am here today to express my serious concerns regarding the Antibiotics Preservation Act, H.R. 7285. The subtherapeutic use of antibiotics in livestock feed is a critical issue which I have been monitoring for several years. I am primarily concerned about the prematurity of this legislation in view of the absence of information supporting the claims that the subtherapeutic use of antibiotics reduces the efficacy of antibiotics in humans. The possibility that human health may be jeopardized because of this particular livestock management practice disturbs me, yet Congress should proceed with caution on legislation which is clearly a reaction to theoretical risks, not clear and present dangers posed on the American public. As a member of the Committee on Agriculture and Chairman of the Subcommittee on Livestock and Grains, I must emphasize this in light of the havoc to be created in the livestock industry. I urge this Subcommittee to proceed cautiously.

Antibiotics in animal feeds serve to promote animal health. A healthy animal produces a tastier and more nutritious product more efficiently. This efficiency is passed on to the consumer in the form of lower prices. The imposition of this ban would be occurring at a time when the farm economy is in a precarious situation. The livestock industry especially at this point is unable to realize a profit, returns are substantially below production costs.

This Congress has recognized the necessity to gather information to determine the scientific, economic, and social implications of a ban of the subtherapeutic use of antibiotics in animal feeds. For example. The Agriculture, Rural Development, and Related Agencies Appropriation Bill of 1980 appropriated $1.5 million for research to generate new epidemiological information by comparing the health of humans with extensive exposure to animals, and/or their products, receiving antibiotics at the subtherapeutic level with the health of comparable individuals not so exposed. This study [redacted] is to be designed in consultation with qualified epidemiologists available through the National Academy of Sciences. In light of the lack of substantial evidence, this solution, further and more definitive research, appears to be the most appropriate course to follow. I question a rash prohibition of the use of antibiotics in animal feeds when the correlation between their use and development of more resistant pathogens in humans has not been adequately investigated.

The Federal Government should encourage further investigation into the uses of antibiotics. At the same time, it is also in the best interest and also a responsibility of the pharmaceutical companies who manufacture these products and other animal health care products to explore other avenues to attain the desired effects in the event research proves a correlation between use of antibiotics in feed and the development of more resistant pathogens. The economic chaos in the livestock industry that would erupt if antibiotics were prohibited necessitates this type of research and intense investigation of present practices.

Antibiotics are used in animal feeds as a nutritional supplement, to treat disease, to prevent disease, to increase weight gain, and to improve feed conversion efficiency. Maintaining animal health rather than restoring animal health when necessary proves to be more efficient. These antibiotics eliminate organisms that compete with the host animal for nutrients and reduces animal dietary requirements. Without these production advantages consumers will ultimately be paying in the marketplace for the loss of efficiency.

This legislation implies that the use of antibiotics at the subtherapeutic level serves only the covetous needs of the livestock producer. If a ban were applied, the first year would be marked by a rather dramatic downturn in livestock production. Producers' costs would increase because of the loss of feed conversion efficiency and thus, because of these increased costs, there would be a decrease in production which precipitates a rise in food prices. Chase Econometrics Associates estimate a rise in the Consumer Price Index for food of 1.3 to 3.7% during the initial year of the ban. This increase would be a direct result of 5-10% decrease in Broiler production, 3-8% decrease in Turkey production, 1.1% decrease in Pork production (expected to remain at this low level at least 4-5 years), and a decrease in feed grain prices due to reduced demand.

This legislation would also place an unfair burden on the small farmer and possibly force some out of business. The small producer

will be forced to compete with the large producers in the face of increases in inputs required to produce the same unit of output, due to poorer feed conversion, increased sicknesses and death losses.

Furthermore, the economic impact, according to Chase Econometric Associates, extends past the farm into a variety of labor forces. For example, the employment in meat packing, trucking, and warehousing sectors of the economy would decrease and those who remain employed would pay more for less meat.

In consideration of the ramifications of H.R. 7285 it is essential to understand the structure of the modern farm. Animal husbandry practices have changed drastically over the past twenty years. The size of farms has grown to tremendous proportions. A single diseased heifer can start an epidemic among 1000 cows in the close confines of the modern feedlot. It is even more critical in the case of poultry and swine whose large scale production is experienced in much closer quarters.

I must stress to this Subcommittee to consider the basis for their judgment on this legislation. Is there indeed adequate information at this time on the subtherapeutic use of antibiotics in livestock feeds to legislate such a ban? I am dedicated to assuring our citizens of safe and nutritious food products. I urge this Subcommittee to encourage further research in these areas so that this priority can be maintained.

Mr. **Waxman**. We very much appreciate your testimony to us and the strong views which you have expressed to us, and we share your desire for us to act cautiously and responsively as we approach something that could have great economic consequences for the people of this country.

Now that the National Academy of Sciences has determined that the type of epidemiological study your committee requested is not feasible, what kind of other studies do you think could be conducted?

Mr. **Rose**. Mr. Chairman, I don't have a concise technical answer to that question, and that is the key question. I would be most happy to participate in a search for that. I was under the impression that the National Academy had suggested about four different studies that they felt should be made. They might be considered and should be looked at carefully. Your committee and the staff may come up with others, I do defer to that, if you please.

Mr. **Waxman**. I haven't seen the Chase Econometrics Associates study which you cite. Do you know if the figures in it reflect the termination of the use of antibiotics or a substitution of other drugs for antibiotics?

Mr. **Rose**. I am afraid it assumes a termination, and on that basis is probably not as accurate as one would be if there were substitution.

Mr. **Waxman**. If we turn to substitution for these antibiotics, do you have any idea whether there would be economic loss of great consequence to the meat industry?

Mr. **Rose**. I would be very much in favor, Mr. Chairman, of turning to substitutes, were we to prove and to show that what we are doing now is improper and unhealthy and dangerous to the American consumer. But it appears that in many areas—and I have gone through this with nitrites in preserving meat in the cured meats as well—that one of the first questions we always seem to ask is, well, what about substitutes, before the full evidence is in on the primary substances that are being used? I would ask that certainly we should serarch for effective substitutes, but should keep in mind that that search for substitutes not be interpreted as a guilty verdict against what is being primarily used.

Mr. **Waxman**. Are these substitutes less desirable from the perspective of the meat industry, and why, if they are?

Mr. **Rose**. I think that that is a broad question that would require us to look at all segments of the meat industry and all of the presently used antibiotics in various animals and various animal feed situations, and then reach a conclusion as to what the cost-benefits and benefits of the substitute would be. I am quite sure that there are substitutes for antibiotics that can be used. I happen to be a great fan of antibodies naturally produced and stimulated in animals, as in the human body, as all animal bodies do.

Some of my friends in the drug companies get a little nervous when I talk about stimulation of antibodies as opposed to antibiotics, but it is clear that research and work needs to be done in this whole area to discover the mechanisms and to assess the risk, and I think any discussion about substitutes is really premature,. until the real danger is assessed.

Mr. **Waxman**. I appreciate your suggestion to us that we approach this cautiously. We have some scientific witnesses that will be heard today. I am interested in pursuing with them the extent of the danger, if any, and pursuing with people in the agricultural community the desirability or lack of it for these alternatives that may also be available that may not offer any potential harm at all to the public health.

I want to thank you for being with us.

Mr. **Rose**. Can I make one last comment, Mr. Chairman? I would hope that in this matter that we could rise above what so often happens to our beliefs system when we engage in an emotional area that might be harmful to humans. I don't want anybody harmed. I don't want any individuals in this country to be adversely affected by meat or handlers of meat that have been exposed to antibiotics.

Some would say that this is an emotional subject that people are going to choose sides on based on either economic factors or emotional beliefs, the economics of whether or not it hurts the meat industry, the economics of whether or not you are manufacturing the currently used antibiotic that the meat industry is using, the economics of whether or not you have just come up with a substitute that would replace the currently used antibiotic that the meat industry is now using.

We need to rise above all of those concerns, those levels of doubt, and reach a scientific plateau where we can make this decision just as objectively as we can, and I say that as the chairman and the past chairman of two committees whose primary responsibility was to encourage meat production. But the meat industry does not want bad things happening to the consumers of its meat. It does not like bad publicity either from being accused of harming people or actually harming people, and the drug companies are the same way.

I have talked too long.

Mr. **Waxman**. We certainly are not here to hurt any industry or to involve ourselves in what are emotionally felt views. Our job as legislators is to hear all the views, weigh them and decide the policy questions that have to take into consideration the impact of any change we might make in the present situation.

Mr. **Rose**. Thank you, Mr. Chairman.

Mr. **Waxman**. Dr. Carter.

Mr. **Carter**. Thank you, Mr. Chairman.

It is indeed a pleasure to welcome you here today, Mr. Rose, a distinguished Member from North Carolina with whom I served for many years. I know him to be calm and cool as the usual thing and to give commonsense advice. Commonsense is the rarest of all commodities perhaps. I think that our work here today has shown you to be quite knowledgeable in this area, and I commend you on your presentation.

By the way, you don't feel that the likelihood of the production of an andromeda strain, as you say, by the use of small doses of antibiotics to keep down disease in livestock and also to increase growth as they are supposed to do, you don't think that a strain could become resistant to those antibiotics and then engulf the world in a terrible disease worse than the bubonic plague or something of that nature?

Mr. **Rose.** Dr. Carter, I would say that I would hate to make the flat statement that some quirk of nature or of genetics might not some day cause any number of calamaties to occur on humanity.

Mr. **Carter.** Yes, sir.

Mr. **Rose.** The combinations of emissions from automobiles in the air might some day create an andromedous strain of chemical reagents that would choke us all without our knowledge that it was about to occur, and I am sure we are all aware of the potential of automobile emissions for harming people. But I don't see that there is any evidence that it is occurring now. We should monitor it. We should be cautious that it not occur, but not throw the baby out with the bathwater.

Mr. **Carter.** Would you think perhaps that this, as another health problems from the disease-of-the-week club, those presented consistently by groups who get great attention from furthering such legislation and backing it and being angels thereto for its passage?

Mr. **Rose.** I wouldn't dare attribute any intentions other than the highest concern for the public to John Dingell's reason for introducing this legislation.

Mr. **Carter.** There are others of us who have doubts about that.

I might say to my friend that by giving antibiotics ourselves as physicians to humans, penicillin, tetracycline, and so on; often the bacteria in the humans becomes resistant to that antibiotic, and that was known long before antibiotics were ever given cattle, pigs, chickens, turkeys, or whatever, so it is possible that this might present a problem, that if it does, we want to do something about it. But I think that we need a firmer basis on which to formulate any legislation.

Mr. **Rose.** May I respond briefly to what you said? You absolutely are right, and the literature, I am sure, is full of evidence where antibiotics have been fed to animals to counteract specific diseases, and that feeding has occurred over long periods of time at subtherapeutic dosages, that resistance can occur.

But our evidence that we found from what you have read here, when you are talking about a subtherapeutic as opposed to a therapeutic, when you are dealing with a subtherapeutic feeding of antibiotics, it seems to be a mechanism in the case of tetracycline that has not allowed resistance to occur. We don't understand that mechanism. And we should study it before we throw out tetracycline, is what I am saying.

Mr. **Carter.** I feel you are right. The term andromeda strain, of course, really applies to a strain of bacteria. There is a book written about it—I recall reading some years ago—but not to a chemical.

I thank the gentleman for his testimony.

Mr. **Waxman.** Thank you, Dr. Carter.

Mr. Dannemeyer?

Mr. **Dannemeyer.** I appreciate the point of view. My question is, do you know of any studies which indicate on what happens to the penicillin after it is consumed by the chicken. Can they, by test, find it in the meat of the chicken?

Mr. ROSE. From being a lawyer and politician and not a chemist, I have to tell you I don't know—I couldn't quote to you those instances when they give chickens penicillin, and I am sure that if chickens were fed any antibiotics, or many antibiotics, that there are devices today that could detect their presence, especially if they were fed in therapeutic levels.

Mr. DANNEMEYER. You don't know the answer to that?

Mr. ROSE. I don't really know the answer.

Mr. DANNEMEYER. Thank you.

Mr. WAXMAN. We very much appreciate your point of view and your being with us today.

I would like to now call forward two members to testify before us as a panel, Dr. Thomas O'Brien, Peter Bent Brigham Hospital, and Dr. Dwayne C. Savage, University of Illinois. We are hoping that you will explain to us how resistance develops and how, if it can be, it is transferred to man.

STATEMENTS OF THOMAS O'BRIEN, M.D., PETER BENT BRIGHAM HOSPITAL, AND DWAYNE C. SAVAGE, M.D., UNIVERSITY OF ILLINOIS

Dr. O'BRIEN. Thank you, Mr. Chairman, and members of the committee, for the chance to comment and review some of the concepts that are involved in these issues.

The life cycle of the bacterial cell is very similar to the life cycle of our own cells. It starts with the genetic information in the DNA for making the proteins. The proteins are then synthesized on the ribosomes, and the proteins, once synthesized, make everything else the cells need, including the membrane, cell wall, and so on. So there is a similar life cycle in the patient and in the bacteria.

There are any number of chemicals that could interrupt this life cycle in the bacteria at specific points, but they would be no good as antibiotics, because they would do the same to the patient's cells. The beauty of the antibiotics, is that each selectively sabotages some very specific target site in this life cycle of the bacterial cell, without doing it at all, or to a very small extent to the analogous step in the life cycle of the patient's cell.

So these target sites, these specific points where there is an opportunity for the antibiotic to act selectively, represent our real heritage from the antibiotic era. In retrospect the discovery of each truly new antibiotic was, in fact, the discovery of one of these target sites, and approximately a dozen emerged in the 1940's and 1950's.

The last of these, the last truly new antibiotic marketed for human use with a truly new target site was refampicin in 1960. So there is, as I believe Representative Dingell mentioned, there is a declining rate of discovery of these target sites, suggesting they are a limited resource and that we cannot go on finding others.

The concern is that the reserve of target sites is disappearing. They are our only hold on the bacteria, are all that separate us from what you might call the medical dark ages—before antibiotics. They are being lost, because one by one they are being blocked.

The loss of a target site happens because the bacterial cell gets a gene which makes a specific protein, which destroys that antibiotic and keeps it away from the target site. So one by one, as these genes are acquired by bacterial cells, they lose vulnerability to the antibiotics.

How are these genes acquired? One bacterial cell gets them from another, and this is where the plasmids come in. The plasmids are genetic material, are DNA that carry multiple genes for antibiotic resistance and for other things, too. They have the remarkable property of being transferred from one bacterial cell to another and then being carried in the progeny of the new recipient cell.

So these are the ultimate units that we want to follow: The prevalence of antibiotic-resistant genes in bacterial populations mostly carried from species to species by these now ubiquitous plasmids.

I think it is worth while considering for a moment the medium through which the plasmids are moving. They are moving through literally a sea of bacteria. Look at it another way: Each of us, every human being, every animal, is a fairly complete bacterial ecosystem in that we all have literally billions of bacteria growing in us and on us——

Mr. CARTER. Trillions.

Dr. O'BRIEN. All right; trillions of bacteria growing in us and on us, and we exchange these to some degree. When you shake hands with a visiting constituent, you get a reinfusion of bacteria from back home. If you open a piece of chicken from the supermarket package, you undoubtedly pick up some bacteria from that animal source.

And these multiple ecosystems, with competing bacterial strains in them all interconnect throughout the world. There is an interconnecting system of bacteria with very few apparent barriers through which these plasmids can move with their resistant genes throughout the world.

I would like to make two other points about the effect of antibiotics on these bacterial populations. There are short-term effects, and long-term effects. The short-term effect that exposure to antibiotics has on a mixed population of competing bacteria, is due to the enormous explosive growth potential of the bacteria. If you take a billion, or a trillion, bacterial cells that are susceptible to an antibiotic, and one cell that is resistant to the antibiotic, mix them together and treat with the antibiotic, all of the susceptible bacteria will be killed. And because the sole surviving resistant strain can multiply every 20 minutes, its logarithmic growth will mean that by the next day, that space, whatever it was, can now be occupied by a trillion cells that are all resistant. It is an extremely dynamic situation in which a very few or even one of the right kind of resistant bacteria in the proper milieu, can be explosively amplified by the selection pressure of antibiotics. That is one kind of effect, the short-term effect, of antibiotics.

The long-term effect is something I think we are just beginning to become aware of, and that is that these plasmids, like all other genetic material, evolve over a period of time and, if continually exposed to antibiotics, they remold themselves. They may start out with one resistant gene and over a period of time pick up another one, two, three, four, five—they may end up with genes to make resistance to six different antibiotics, or even more, as kind of an evolutionary process. They may also acquire genes that are favorable to those particular plasmids in other ways, permit them to live in the bacterial cell for longer than they would otherwise. So there is this kind of evolutionary change over a period of time that seems to make worse plasmids, more menacing plasmids, with potential for greater damage.

The point that strikes me about all of this is that the changes in time, the evolutionary changes, as far as we can see now, must relate almost entirely to the total prior exposure of all bacteria to antibiotics. Possibly if you could get to the total number of bacteria exposed to antibiotics previously it would be a kind of basic mathematical unit for this evolutionary pressure for developing evolving plasmids.

If that holds up, and if it turns out—and I think there is pretty good evidence now that there really is no effective compartmentation between the flora of individuals, and individuals and animals, then the ultimate distribution and prevalence of antibiotic-resistance genes in bacteria would be a consequence of the total prior exposure of bacteria to antibiotics probably without much distinction as to where that happened.

The one development I would pick out, there are others, but most striking is what happened to Hemophilus influenzae. Hemophilus influenzae, as Dr. Carter knows, is the most common cause of bacterial meningitis in children. After 30 years of exposure to penicillin all over the world no strains ever developed resistance, and you might have thought over that time span, if it were going to happen, it would have happened. Yet, 5 years ago, after 30 years of exposure, strains began to appear that had the right gene and right plasmid finally evolved—to destroy pencillin and ampicillin. Ampicillin had previously been the drug of choice and very good for the treatment of the disease, and now it could no longer be relied on——

Mr. **Carter**. I guess the good doctor knows that resistant gonorrhea did develop, and that pencillin was no longer effective in the cases of treatment of gonorrhea, even as far back as 1947. Is that not correct?

Dr. **O'Brien**. Moderate levels, yes, but the first documented—case of a gonococcus acquiring plasmid resistance was 4 or 5 years ago, after a long experience. So that there appears to be for both these cases, both the gonococcus and hemophilus influenza, finally resistance developing after a very long period of evolutionary pressure.

My concern would be this would be related to evolutionary pressure from antibiotic usage everywhere, and not in a particular species.

Thank you.

Mr. **Waxman**. Thank you very much.

Dr. Savage?

STATEMENT OF DWAYNE C. SAVAGE, M.D.

Dr. **Savage**. Mr. Chairman I am afraid I have to appear before you as something of a troglodyte. Now that Dr. O'Brien has told you of something known, I am going to talk about some things that are not known. I would like to take a particular focus, and that is on all of these trillions of microorganisms that live in and on the body and discuss what we don't know about their resistance to antimicrobial drugs.

I have a written statement which, with your permission, I will read parts and summarize parts for the sake of brevity. [See p. 324.] This statement is condensed and somewhat modified from appendix D of the report of the committee of the National Research Council on Human Health Effects of Subtherapeutic Antibiotic Use in Animal Feeds. For convenience of presentation, some supporting evidence and the literature citations given in that document have been omitted. In the statement, I focus on two issues:

One. Antibiotic resistance of microorganisms in the gastrointestinal tracts of certain animals and man and its transfer, and

Two. How subtherapeutic levels of antibiotics affect the composition of the so-called "normal flora" of the gastrointestinal tract.

To deal with the issues, I wish first to present to you some details concerning the composition of the flora of the gastrointestinal tract.

Many persons with some familiarity with the problem often speak of a "normal gut flora." In my opinion, however, that term is confusing. Much of the confusion involves the word "gut," which usually means "intestine." Much evidence supports the hypothesis that most higher animals, including cattle, swine, and chickens—possibly even humans—have "gastrointestinal microbiota" composed of indigenous microbes colonizing specific habitats located throughout the gastrointestinal tract, not just in the gut. I shall amplify that concept.

First, however, I wish to note that you will hear from me little about antimicrobial resistant *Escherichia coli*. Much evidence has been published on how antibiotics influence the population levels and antimicrobial resistance in *E. coli* and its relatives—for example, Salmonella species—in the intestinal tract. *E. coli* and some of its relatives are important pathogens. Moreover, probably because it is easy to culture and manipulate in vitro, it has also become the major bacterial tool of molecular biologists. Thus, there is great interest concerning its resistance to antimicrobial agents. As documented below, it can be recognized as a member of the "normal gut floras" of many species of animals. It is usually a minority member of such floras.

Studies of the antimicrobial resistance of *E. coli* have been reported in depth. However, the findings of these studies may be inadequate to demonstrate how predominant flora may interact with antimicrobial drugs. Consequently, I have chosen to minimize discussion of *E. coli* and to emphasize findings and concepts concerning the types of bacteria that predominate in the "normal gut flora."

I will now summarize part of the statement. The next section deals with population levels and localization of microorganisms in the gastrointestinal ecosystem.

Microorganisms of many types have been isolated from the contents of the stomachs of humans and swine and from the crops of chickens—the rumen microbiota is discussed later. Most of the types isolated should probably be regarded as transients since the stomachs of most animals undoubtedly empty more rapidly than microorganisms can multiply. Thus, microbes in the lumen pass out of the stomach with the contents. Nevertheless, certain types can be regarded as autochthonous to habitats in the area. *Lactobacillus spp.* at high population levels—10th to the 9th organisms per gram of mucosa—can be cultured from the crops of chickens. Likewise, *Lactobacillus spp.* and *Candida spp.* can be cultured at comparable population levels from the squamous epithelium in the pars oesophagia of swine. Although such organisms are usually found in the stomachs of humans as well, much more research is needed to test the hypothesis that humans have an indigenous gastric microbiota.

The small intestines of humans and chickens—and undoubtedly also swine and calves—also yield many microbial species. Most of the organisms are probably transients, especially in the upper two-thirds of the bowel where peristalsis moves luminal content much more rapidly than microbes can multiply. Microbes of types found in the large bowel may be identified, occasionally at high population levels, in cultures from the lower third of the small intestine, where the content moves somewhat sluggishly and may not move at all for a time. Such organisms may be indigenous to the region or may be contaminants from the large bowel that have crossed the ileo-cecal valve into the area. In chickens, however, microbes seen adhering to the epithelium of the small intestine are undoubtedly indigenous to that area.

The large bowels of humans and the ceca and colons of swine and chickens contain enormous populations of microorganisms—more than one times 10th to the 11th microbes per gram dry weight of content. The contents of those regions move sluggishly and allow ample time for microbial multiplication. The populations are composed primarily of bacteria that cannot multiply in atmospheres containing oxygen. Indeed, many of the species are intolerant of oxygen and are killed by exposure to it or to growth media or diluting fluids with oxidation—reduction potentials above certain negative levels. Human feces yield up to 400 species in as many as 40 microbial genera. The vast majority of the species are oxygen-intolerant anaerobic bacteria. More than 99 percent of the total microbial population obligately gains its energy through anaerobic processes. In the gastrointestinal ecosystem of humans, facultative bacteria—that is able to use both aerobic and anaerobic processes to generate energy—such as *E. coli* are usually outnumbered by the anaerobes by as much as 1,000-to-1. The systems of swine and chickens are undoubtedly similar.

[Testimony resumes on p. 336.]

[Dr. Savage's prepared statement follows:]

STATEMENT OF DWAYNE C. SAVAGE, M.D., UNIVERSITY OF ILLINOIS

This statement is condensed and somewhat modified from Appendix D of the report of the Committee of the National Research Council on Human Health Effects of Subtherapeutic Antibiotic Use in Animal Feeds. For convenience of presentation, some supporting evidence and the literature citations given in that document have been omitted. In the statement, I focus on two issues:

1) Antibiotic resistance of microorganisms in the gastrointestinal tracts of certain animals and man and its transfer, and

2) How subtherapeutic levels of antibiotics affect the composition of the so-called "normal flora" of the gastrointestinal tract.

To deal with the issues, I wish first to present to you some details concerning the composition of the flora of the gastrointestinal tract.

THE GASTROINTESTINAL ECOSYSTEM

Many persons with some familiarity with the problem often speak of a "Normal Gut Flora." In my opinion, however, that term is confusing. Much of the confusion involves the word "gut," which usually means "intestine." Much evidence supports the hypothesis that most higher animals, including cattle, swine, and chickens (possibly even humans), have "gastrointestinal microbiota" composed of indigenous microbes colonizing specific habitats located throughout the gastrointestinal tract, not just in the gut. I shall amplify that concept.

First, however, I wish to note that you will hear from me little about antimicrobial resistance in Escherichia coli. Much evidence has been published on how antibiotics influence the population levels and antimicrobial resistance in E. coli and its relatives (e.g., Salmonella species) in the intestinal tract. E. coli and some of its relatives are important pathogens. Moreover, probably because it is easy to culture and manipulate *in vitro*, it has also become the major bacterial tool of molecular biologists. Thus, there is great interest concerning its resistance to antimicrobial agents. As documented below, it can be recognized as a member of the "normal gut floras" of many species of animals. It is usually a minority member of such floras.

Studies of the antimicrobial resistance of E. coli have been reported in depth. However, the findings of these studies may be inadequate to demonstrate how predominant flora may interact with antimicrobial drugs. Consequently, I have chosen to minimize discussion of E. coli and to emphasize findings and concepts concerning the types of bacteria that predominate in the "normal gut flora."

POPLUATION LEVELS AND LOCALIZATION OF MICROORGANISMS IN THE GASTROINTESTINAL ECOSYSTEM

The Microbiota of the Stomach

Microorganisms of many types have been isolated from the contents of the stomachs of humans and swine and from the crops of chickens (the rumen microbiota is discussed later). Most of the types isolated should probably be regarded as transients since the stomachs of most animals undoubtedly empty more rapidly than microorganisms can multiply. Thus, microbes in the lumen pass out of the stomach with the contents. Nevertheless, certain types can be regarded as autochthonous to habitats in the area. Lactobacillus spp. at high population levels (10^9 organisms per gram of mucosa) can be cultured from the crops of chickens. Likewise, Lactobacillus spp. and Candida spp. can be cultured at comparable population levels from the squamous epithelium in the pars oesophagia of swine. Although such organisms are usually found in the stomachs of humans as well, much more research is needed to test the hypothesis that humans have an indigenous gastric microbiota.

The Microbiota of the Small Intestine

The small intestines of humans and chickens (and undoubtedly also swine and calves) also yield many microbial species. Most of the organisms are probably transients, especially in the upper two-thirds of the bowel where peristalsis moves luminal content much more rapidly than microbes can multiply. Microbes of types found in the large bowel (see below) may be identified, occasionally at high population levels, in cultures from the lower third of the small intestine, where the content moves somewhat sluggishly and may not move at all for a time. Such organisms may be indigenous to the region or may be contaminants from the large bowel that have crossed the ileo-cecal valve into the area. In chickens, however, microbes seen adhering to the epithelium of the small intestine are undoubtedly indigenous to that area.

The Microbiota of the Large Intestine

The large bowels of humans and the ceca and colons of swine and chickens contain enormous populations of microorganisms (more than 1×10^{11} microbes per gram dry weight of content). The contents of those regions move sluggishly and allow ample time for microbial multiplication. The populations are composed primarily of bacteria that cannot multiply in atmospheres containing oxygen (Table 1). Indeed, many of the species are intolerant of oxygen and are killed by exposure to it or to growth media or diluting fluids with oxidation--reduction potentials above certain negative levels. Human feces yield up to 400 species in as many as 40 microbial genera. The vast majority of the species are oxygen-intolerant anaerobic bacteria. More than 99% of the total microbial population obligately gains its energy through anaerobic processes. In the gastrointestinal ecosystem of humans, facultative bacteria (i.e., able to use both aerobic and anaerobic processes to generate energy) such as *E. coli* are usually outnumbered by the anaerobes by as much as 1,000 to 1. The systems of swine and chickens are undoubtedly similar (Table 1).

TABLE 1

Principal Bacterial Genera Reported to be Present in the Feces or Content of the Large Bowels of Swine, Chickens, or Humans[a]

Predominant Genera[a]

Swine	Chickens	Humans
Eubacterium	*Eubacterium*	*Eubacterium*
Peptostreptococcus	*Bacteroides*	*Bacteroides*
Clostridium	*Fusobacterium*	*Fusobacterium*
Lactobacillus	*Peptostreptococcus*	*Peptostreptococcus*
Propionibacterium	*Bifidobacterium*	*Ruminococcus*
Streptococcus	*Gemminger*	*Coprococcus*
Peptococcus	*Clostridium*	*Bifidobacterium*
Megasphaera	*Propionibacterium*	*Clostridium*
		Lactobacillus

Minor Genera[b]

Swine	Chickens	Humans
Bacteroides	*Staphylococcus*	*Acidaminococcus*
Bifidobacterium	*Streptococcus*	*Staphylococcus*
Treponema	*Escherichia*	*Propionibacterium*
Veillonella		*Peptococcus*
Escherichia		*Desulfomonas*
		Succinivibrio
		Streptococcus
		Escherichia

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[a] Population levels of many species exceed 1×10^9 organisms per gram of content. Most exceed 1×10^{10} organisms per gram.

[b] Population levels less than 1×10^9 organisms per gram of content. Many species have levels of less than 1×10^8 organisms per gram.

The Microbiota of the Rumen

The biota in the rumen of adult bovine and ovine animals is also highly complex, consisting of protozoa and bacteria at enormous population levels (total levels greater than 1 x 10^{11} organisms per gram dry weight of content). Most of the bacterial species in the rumen belong to anaerobic genera. Some of them are similar to those found in the large bowels of monogastric animals (Table 1); others are undoubtedly unique to the ecosystem of the rumen. Facultative organisms such as E. coli are usually not present at all or present only at low population levels. The biota of the remainder of the bovine intestinal tract has not been characterized.

Summary

All mammalian and avian species have microbial floras that are indigenous to their gastrointestinal tracts. In humans, calves, swine, and chickens, climax floras, such as might be found in healthy adults, contain primarily anaerobic bacteria in most habitats of the tract. Under normal conditions those anaerobes vastly outnumber facultative microbes such as E. coli. In fact, as shall be seen, in normal, unperturbed systems the anerobes undoubtedly function to restrict the population levels of E. coli and its relatives.

ANTIBIOTIC-RESISTANCE IN MICROORGANISMS IN THE GASTROINTESTINAL TRACT

Investigators interested in E. coli, primarily as a potential pathogen, have provided considerable data on antibiotic-resistance in strains isolated from the intestinal tract. Strains of E. coli with resistance to numerous antibiotics, many carrying transferable plasmids coding for such resistance, can be isolated from calves, swine, and poultry being fed or treated with antimicrobial drugs. Such strains can also be isolated from animals ostensibly not fed or treated with the drugs, but with much less frequency than from animals receiving drugs. In this latter case, however, most investigators have not provided reassurance that these controls have not been in contact with antibiotics, for example, through association with parental animals treated with drugs.

Reliable information of the type available for *E. coli* is virtually unavailable for the bacterial species predominating in the gastrointestinal ecosystem. Anaerobic bacteria of many genera can develop resistance to antimicrobial drugs. This has been demonstrated for organisms from the rumen, from feces of humans and swine, and from the ceca of chickens. Moreover, investigators have demonstrated that plasmids code for resistance to several antibiotics in certain species of intestinal bacteria other than *E. coli*, and that plasmids coding for such resistance can be transferred *in vitro* from donor to recipient strains of a few species of anaerobic bacteria.

Most such information has been gained in studies conducted within the last 4 or 5 years. Indeed, many recent reports on the transmissibility of plasmids in anaerobes appear only as abstracts in the literature. Much of the work concerns anaerobic bacteria as pathogens rather than as members of the indigenous microbiota. Although these efforts provide good indications of gene transmission among the anaerobic members of the gastrointestinal ecosystem, little of the evidence has been gained in such a way that a realistic determination can be made of the proportion of antibiotic-resistant strains in "normal" flora.

ANTIMICROBIAL RESISTANCE IN THE GASTROINTESTINAL MICROFLORA INDUCED BY SUBTHERAPEUTIC LEVELS OF ANTIBIOTICS IN FEED

Indigenous Bacteria of the Gastrointestinal Microbiota

As just noted, reliable information on the proportion of resistant strains in gastrointestinal microbiota is almost nonexistent for the major components of the indigenous flora. Ample evidence supports observations that strains of *E. coli* with resistance to penicillins, tetracyclines, and other antibiotics can be isolated much more frequently from animals fed subtherapeutic doses of tetracycline and penicillin in their diets than from animals eating diets free of the drugs. Indeed, after animals have consumed the diets containing drugs for just a few days, more than 90% of the E. coli strains isolated are resistant to the drugs used in the diets and to other compounds. By contrast, less than 10% of the strains isolated from animals not fed the drugs are resistant to antibiotics. Some efforts have been made to develop such information for a few other types of bacteria that can be cultured from the gastrointestinal tracts of animals.

For example, dietary chlortetracycline has been found to induce resistant strains of Streptococcus faecalis that predominate over sensitive strains in ceca of chickens. Similarly, 90% of the strains of lactobacilli or streptococci isolated from the feces of swine were commonly resistant to penicillin or to chlortetracycline if isolated from animals fed diets containing that drug. By contrast, more than 90% of the same strains isolated from animals not fed the drugs were sensitive to them. However, only the latter of these bacteria types can be regarded as major components of the indigenous flora.

Potential Pathogens in the Gastrointestinal Microbiota

Virtually no information is available on the influence of antimicrobial drugs on the relative proportions and absolute numbers of potential pathogens in the indigenous biotas except for E. coli and its relatives (e.g., Salmonella species). Actually, "pathogen" is difficult to define in reference to the biota. In swine, Treponema hyodysenteriae can cause dysentery only when acting with other anaerobic components of the indigenous biota, none of which are known to be pathogens. Likewise, many other indigenous species have the capacity to cause disease under the right circumstances. In several species of animal, including pigs and chickens, Clostridium perfringens can cause diarrheal disease under certain conditions. In humans and other animals, certain Bacteroides spp. induce abscesses in normally sterile tissues, often in association with facultative bacterial species. Many other species of anaerobic bacteria can cause disease under certain conditions. Most of them are normally present in the gastrointestinal tracts of animals at high population levels. Thus, the question of whether or not antibiotics tend to increase the relative proportions and absolute numbers of potential pathogens is moot.

Persistence of Changes when Selection Pressure is Removed

The duration of resistance when antibiotics are removed from the feed or treatment is stopped has not been determined satisfactorily for most species found in the gastrointestinal tract. E. coli strains bearing drug resistance plasmids may persist in the biotas of animals for months after the selection pressure is removed. Similarly, Streptococcus strains with resistance to chlortetracycline may persist in the ceca of chickens for months after the drug is removed from their diets. Whether or not such findings apply to the majority components of the biota is not known.

INFLUENCE OF SUBTHERAPEUTIC LEVELS OF ANTIMICROBIALS ON THE COMPOSITION OF THE GASTROINTESTINAL MICROFLORA

Much evidence supports an hypothesis, that the gastrointestinal microflora much affects the health and welfare of the animal host. Indeed, it is known that in many animal types the flora influences digestion, absorption of nutrients, resistance to disease and even growth and longevity. Thus knowledge of how antimicrobial drugs affect the composition of the biota is important because changes in the composition of the flora may influence how it in turn influences its hosts' physiology.

Many factors are known to influence the population levels and localization of microorganisms in the gastrointestinal ecosystem (Tables 2 and 3). Some of the forces are exerted by the host, its environment, and diet (the allogenic factors). Some are exerted by the microorganisms themselves (the autogenic factors).

TABLE 2

Some Allogenic Factors Known to Influence the Composition of the Indigenous Microbiota in Certain Regions of the Gastrointestinal Tract

Factor	Possible Region of Influence	Normal Features that Influence Composition of Microbiota
Temperature	Stomach Small intestine Large intestine	Body temperature (37°C)
pH	Stomach Small intestine Large intestine	Acidic Neutral to alkaline Neutral to alkaline
Stasis	Stomach Small intestine Large intestine (including cecum)	Periodic Periodic in lower part of region Prolonged (residence time) especially in cecum
Oxygen	Large intestine[a]	Concentration low, if present at all
Oxidation-reduction potential	Large intestine[a]	Low potential, especially when microbes are present
Enzymes	Small intestine[a]	Pancreatic enzymes present
Bile acids	Stomachs Small intestine Large intestine	Low concentration Conjugated bile acids present Deconjugated bile acids present
Epithelial turnover	All regions of tract	Sloughing of cells necessitates replacement of attached cells but the cells may provide microbial nutrients
Urea	Large intestine[a]	Can be carbon and nitrogen source for certain microbial species
Mucin	All regions of tract	Mucin contributes to the viscosity of the environment and may act as a microbial nutrient
Diet	All regions of tract	The diet provides microbial nutrients and affects the nature of habitats in the tr
Drugs	All regions of tract	Influence is characteristic of the drug(s)
Phagocytic cells	Crypts of Lieberkühn	Microbiota may be phagocytosed (selectivel
Antibodies	All regions of tract	Precise effect on biota not known. Antibody protein may be utilized nutritionally by microorganisms

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[a] Evidence is insufficient to suggest that the factor may operate in other regions.

TABLE 3

Some Autogenic Factors Known to Influence the Composition of the Indigenous Microbiota in Certain Regions of the Gastrointestinal Tract

Factor	Possible Region of Influence	Normal Features that Influences Composition of Microbiota
Volatile fatty acids	Any habitat	Effect dependent upon oxidation-reduction potential
Bacteriocins	Any habitat	Effects uncertain
Nutritional competition	Any habitat	Effects uncertain
Hydrogen sulfide	Probably in large intestine[a]	May depress population levels of some facultative species of bacteria
Adherence to epithelium	Any habitat	Allows microorganisms to colonize areas of the tract where peristaltic rate moves contents more rapidly than bacteria can multiply

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[a] Evidence is insufficient to suggest that the factor may operate in other regions.

The microbiota can alter the forces generated by the host, making them either more or less effective in controlling the biota. Thus, the processes influencing a microbe's ability to colonize a niche in a habitat in the gastrointestinal tract are enormously complex. It is known, however, that the strictly anaerobic bacteria are the most important components of the biota involved in stabilizing established communities in adult animals.

The processes involved in maintaining such stability undoubtedly work most effectively in adult animals with unperturbed indigenous biotas. A system may be perturbed by antimicrobial drugs. Because such drugs perturb the system, they must upset the balance of forces that regulate the biota. The precise factors that are perturbed, especially those affected by subtherapeutic doses of drugs, can only be conjectured. No doubt exists, however, that subtherapeutic doses of both penicillin and tetracycline in animal feeds somehow tip the balance towards resistant strains in the biota of the animal fed the diet.

Humans associating with animals fed subtherapeutic doses of antibiotics may temporarily carry resistant strains of E. coli that are present in the animals. Such bacterial strains may transfer from animals to humans, however, whether or not the animals are fed antibiotics. When antibiotics are removed from an ecosystem, the maintenance of resistance may become an undue physiological burden for some bacterial strains. Thus, they may fail to compete with unhandicapped strains of the same species and eventually decline in prevalence and disappear from the system. At this time, however, these hypotheses can be neither supported nor rejected by evidence provided by studies of the major components of the indigenous microbiota - the strictly anaerobic bacteria.

SUMMARY

Antibacterial drugs such as penicillin and the tetracyclines, when incorporated as growth promotants into the feed of animals, provide a selective

environment in the gastrointestinal tract favoring the proliferation of resistant strains of Escherichia coli, Streptococcus spp., and at least some of the major (strictly anaerobic) bacterial components of the indigenous microbiota. As with E. coli, some strains of strict anaerobes carry genetic information for resistance on plasmids. For a few such bacterial species, the plasmids can be transferred to recipient strains of the same species. Certain strains of Bacteroides may even be able to transfer their plasmids to recipient strains of E. coli and vice versa.

Such information provides limited evidence that the mechanisms of antibiotic resistance in some strains of anaerobic bacteria in the gastrointestinal ecosystem are similar to the mechanisms of such resistance in E. coli. However, it does not reveal anything about the proportion of resistant anaerobic strains that reside in animals receiving drugs in feed. Most importantly, perhaps, it reveals nothing about whether or not such resistance is transferred between microbial species in the gastrointestinal tract and whether or not resistance is maintained in the tract of an animal not being fed or treated with drugs. Information pertaining to these questions is insufficient for the major components of the biota, especially as they interact with each other and their host. Microorganisms in the gastrointestinal ecosystem interact biochemically and genetically with each other and biochemically with their animal host. Such interactions are complex mechanistically and not well understood. Much more evidence is needed before the impact of antibiotics on the system can by understood.

Mr. **Waxman**. Thank you very much. Let me explore some of these points with both of you, if I might.

Can you describe the differences in the effectiveness in humans of antibiotics now and 20 years ago? Has there been a change?

Dr. O'**Brien**. Yes, there has been a change in that there are types of resistance and prevalence of resistance in certain species now that are much greater than they were 20 years ago and some of these we have mentioned as being particularly conspicuous, the gonococcus being one.

There are also new examples of problems that didn't exist before. In our hospital we had entry of a single new plasmid in 1976. Our monitoring systems shows that was not in the hospital before and entered in 1976. It circulated through the hospital widely and it is still there and from the point of view of the hospital, it is an Andromeda plasmid. It has increased the prevalence of multiple resistance, resistance, say, to more than five antibiotics, about threefold since its entry, that one plasmid.

There is every reason to believe that the short-term amplification of that plasmid in our hospital, and this problem, is due to in-hospital use of antibiotics, gentamicin particularly. But the fact there should be such a basically proficient plasmid to pick up this gentamicin resistance gene. I think has to be considered the product of a lot of prior antibiotic usage over the previous 10 or 20 years to cause the evolution of this basic plasmid to make it available to carry this very troublesome gene. That I see as an example of a kind of cumulative effect of antibiotic usage everywhere.

Mr. **Waxman**. Can we assume the cumulative effect would also be a cumulative effect from not only use of antibiotics in treatment, but cumulative effect from antibiotics that are ingested from animals treated——

Dr. O'**Brien**. I think that the long-term evolutionary process that must go on is related fundamentally to enormous numbers of bacteria being exposed repeatedly to antibiotics, and I think the interchange in the system is sufficient between human and human, animal and human so that in the long run it doesn't matter where.

Mr. **Carter**. If you would just yield on that, I believe you admitted that the in-hospital use of antibiotics had caused a resistance?

Dr. O'**Brien**. I think it caused the amplification once it arrived in the hospital. But prior to that——

Mr. **Carter**. And ever since its beginning, antibiotics have caused this. It is an evolutionary process, only the fittest survive, you stated it yourself.

Thank you, Mr. Chairman.

Mr. **Waxman**. Are you saying then that the evolutionary process is a process that is not within an individual but within living organisms, generally speaking, wherever they may be?

Dr. O'**Brien**. From what we know of it, and, of course, it is hard to monitor, but what we know of it it apparently requires, prolonged exposure through millions of generations of bacteria, and probably recycling exposure to different kinds of antibiotics. I think that the interchange between our own flora, one another, and that of animals is so great one wouldn't expect there to be a real separation, that the cumulative use overall would relate to this process rather than the use in particular species.

Mr. WAXMAN. One would think in looking at this problem that we would need to show that there is a residue of antibiotics in the meat from an animal ingested by a human, but from what I understand you are saying that it is not the residue, such as we are often concerned about pesticides' residue in food, it is not like that at all that offers us cause for concern, it is the world of bacteria that is affected to which we are then exposed.

Dr. O'BRIEN. I think that is true. I think that the game is within the enormously complicated population of bacteria that we all carry rather than having much to do with the housing, which is us at one time and animal at another.

And an effect at one given point in time, changes the population. Exposure to antibiotics is a historical event for a bacterial population, changes it so that it is different, has a different potential from then on, even after the antibiotic is gone, long since gone.

Mr. WAXMAN. How would either of you factor in the fact that humans usually take a 10-day course of high-dose antibiotics, while animals take them at low doses and continuously? What is the effect of each of these regimens on resistance?

Dr. SAVAGE. In both cases resistance develops without a doubt. The difference is when therapeutic levels are used properly, under the right conditions of the patient's immunological system functioning properly, the pathogen at question might be repressed so rapidly that it won't have an opportunity to express any resistance that might be there, and the immunological system will take care of any residue of existent organisms in the population.

In other words, therapy with antimicrobial drugs actually is an assist to resistance mechanisms that function normally. Any population of microorganisms will have in it some fraction of resistant organisms to any drug, so the physician is always dependent on the resistance mechanisms. The drug may knock out the major portions; the resistance will hopefully get the existing ones. It is a very delicate balance. In the case of subtherapeutic doses, I think for *E. Coli, Salmonella,* and other species, it is well documented that shortly after these go into the feed, resistant strains can be isolated from the animals, and these persist as long as the drug is in the feed. It is a very complicated issue, but it does take place.

In therapy, if the resistance mechanisms for some reason or another don't repress the resistant population, then you are going to have growth of the resistant organisms and presumably continuation of the infection.

I would like to, just because I have to—I feel compelled to—I have to comment on something Dr. O'Brien said. In his comments, I have a little trouble differentiating theory or hypothesis from what we know. Let me make a case in point. Although microorganisms living on body surfaces, say, in pigs and humans, are similar taxonomically, in the broad sense of the word often there are sharp differences in the capacity or organisms from one animal type to colonize another animal species. In the sense that strains of E. coli from swine, for example, known to cause disease in swine, have specific determinants for colonizing the swine, they will not colonize human beings. The more we learn about the organisms that live on body surfaces, the more we are inclined to believe there are some sorts of evolutionary barriers between the strains of organisms that live in one animal being able to colonize another animal.

For example, what happens if you inject a strain of an alien organism from one animal into a defined system in another animal species; the population very quickly disappears.

The question, though, and this is not known, is whether or not in doing that there is enough time for that organism, if it is carrying a plasmid, to transmit it to organisms that might be living in the animal. That is an unknown. There is some evidence, but it is very hard to interpret.

Mr. **Waxman**. Even if it is true that some bacteria are not transmitted because of immunities that are in the body to whom it would be transmitted, or that there is a propensity for the bacteria to only go to that organism for which it attaches, even if that were true, it doesn't deny the fact there is that constant interchange of bacteria among living organisms to some extent?

Dr. **Savage**. No. I think Dr. O'Brien is absolutely correct. We are passing microorganisms around all the time, by the millions.

Mr. **Carter**. Hopefully, Mr. Chairman, if you would permit, we are not getting microorganisms in our meat; hopefully, it is cooked and sterilized before we get it.

Mr. **Waxman**. What would be the impact of that, if we were talking about raw meat? We cook meat generally. Would that destroy any organisms that we might otherwise pick up?

Dr. **Savage**. It is one of the sources of *Salmonella* in humans. Poultry is a source, and very often people will cut up their fresh chicken on a board and then cook the chicken. They don't get sick from the chicken, but then they cut a salad on the board and pick up the *Salmonella*. They eat the salad raw, and get it indirectly from the poultry. This happens fairly frequently. I don't know whether it happens with red meat. I know personally of those documented cases.

Mr. **Waxman**. We want to act, of course, responsibly, and what we have before us is a theory, and, of course, science works on hypothesis that tends to be proved or not proved, and we evaluate the evidence, and we evaluate the hypothesis in relationship to that evidence.

Can we ever know enough to indicate that there is a harmful effect to humans because of the immunization we are getting from antibiotics used in animal feed? It seems to me what you are describing is something that, if the theory were correct, may well exist in reality, but unknowable and unprovable.

We have had suggestions to us this morning that we should have further tests. Are there further tests that can reach a more definitive conclusion?

Dr. **O'Brien**. My focus has been on the behavior of bacterial populations and observations in experimental conditions and also in animals as to how plasmids develop and how antibiotic resistance is transmitted, and I don't think that is theoretical. I think that the study of the behavior of the bacteria, themselves, carries a very powerful indication as to how they must be functioning, so I don't think it is entirely theoretical. On the basis of what we already know from that kind of evidence, I think it would be a very major concern.

Mr. **Waxman**. Let's look to the future. If resistance to antibiotics continues to increase, what are the consequences?

Dr. **O'Brien**. The consequence will be two-fold, and I think Dr. Carter would be able to reinforce this. First of all, as resistance becomes more prevalent in the bacteria infecting patients, the patient's chances of getting the right therapy from the beginning of his infection is diminished because it is harder to guess what one possibly might still work. So there will be treatment failures from an initial high prevalence of resistance that can't be anticipated.

Subsequently, when the organism is identified, there will probably be agents that will be effective, but they will limit the physician's scope, and sometimes they will be more toxic and certainly they will be more expensive than the agents that might have been available had there not been resistance.

Dr. **Savage**. I would like to take a slightly different approach to this. A good deal of evidence does exist in the literature that once a particular selective pressure is lifted, antimicrobial-effected pressure, the level of resistance declines. Some of the best evidence comes from a problem of the 1950's, when pencillin-resistant staphylacoci were a tremendous hospital problem; they are less so now. Once more judicious use of antimicrobials in that particular therapy was adopted, then the resistance patterns began to decline in hospitals all over the world.

There are mechanisms that make it unprofitable for an organism to carry a plasmid if there isn't selective pressure to pull that plasmid. We don't understand many of those. This is ecological research and people don't often work on things of that sort or want to work on them. But it is true, nevertheless, that judicious use of antimicrobial drugs could help the resistance problem, and discontinuing use of it for some time might see a decline in resistance in hospital strains or clinical strains, and then perhaps the drug could be introduced sometime later.

I have problems with this whole issue, personally, and I would like to make a personal statement, if I might.

I fear that so much attention on antibiotics in cattle feed might divert attention away from what I consider to be a very serious problem of injudicious use of antibiotics drugs in practice. There are dermatologists—I don't want to cite them specifically, but I shall—who use essentially subtherapeutic levels in patients for 10 or 15 years for acne. And, by the way, tetracycline is the drug of choice.

I could go on with that kind of thing. If you try to carve out the two issues on the one hand—antimicrobial resistance and injudicious use of drugs—then it is important for me to come down on the side of looking hard at how physicians are using antibiotics. Not doing so may divert attention away from what could be the most important problem. We don't know enough about the transfer between animals and human beings.

Mr. **Waxman**. Dr. Carter?

Mr. **Carter**. Thank you, Mr. Chairman. I was very much interested about the flora of the large intestine. What does the common test of water show? What is that——

Dr. **Savage**. In this country it is *Escherichia coli*.

Mr. **Carter**. So it is considered quite a usual part of the flora of the intestine?

Dr. **Savage**. I would add some people do advocate using enterococci, because *E. coli* isn't always present in the large bowel in some individuals and could be misleading.

Mr. **Carter**. And we talk a lot about tetracycline. I wonder—I know you gentlemen are familiar with all of these things; physics, and so on—and I would like for one of you to show me the formula for tetracycline. Could you do that? I haven't looked at it for a long time. But if I remember correctly, it is in the form of a hexagon like this; is that correct?

Dr. **Savage**. Yes.

Mr. **Carter**. What is the difference between this and Terramycin?

Dr. **Savage**. That is the benzene ring.

Mr. **Carter**. I know, but this is a tetracycline, basic "tet." If we go off here with oxy, what do you call that?

Dr. **Savage**. Oxytetracycline.

Mr. **Carter**. What is the name for it?

Dr. **Savage**. Terramycin.

Mr. **Carter**. And if we go further, we have Aureomycin. All right. Thank you gentlemen for that.

Of course, we must admit that anthrax is one of the bacteria which does occur in animals and might be affected by giving the animal antibiotics, and we might possibly get a strain that would be terribly infective to the human, but rather doubtful, I would think.

What else might cause trouble, disease in the human?

Dr. **O'Brien**. Enterobacteriacae.

Dr. **Savage**. These are probably not the most common, now.

Mr. **Carter**. These are certainly some of the most deadly. Is that correct?

Dr. **Savage**. Yes.

Mr. **Carter**. Do you really feel that we have done enough study on this to legislate? Is that correct?

Dr. **Savage**. That is my opinion.

Mr. **Carter**. Yes, sir, but you think we should go ahead and pass this legislation barring the use of antibiotics?

Dr. **O'Brien**. On balance, I would say yes.

Mr. **Carter**. Except I suppose if we had a herd infected with anthrax, you would permit it in that case?

Dr. **O'Brien**. I don't think the intent is to restrict therapeutic antibiotics; I think it is only their addition to the animal feeds.

Mr. **Carter**. You spoke of the evolutionary changes. Of course, evolutionary changes occur with or without antibiotics; is that not correct? And an antibiotic given to an animal might alter its evolutionary trend. Is that correct? And it would alter it in many cases, but it would only alter it—because the evolution is continuous, anyway, the effect of one antibiotic in the gut might cause something, is that correct—an alteration?

Dr. **O'Brien**. I am sure they are subject to a variety of evolutionary pressures, but it is hard to imagine anything as potent as antibiotics.

Mr. **Carter**. Some years ago, there was a famous Austrian who developed a theory that controlling the intestinal flow also improved a person's health, and he mentioned, I believe, lactobacillus, the bacterium.

Dr. **Savage**. I don't think the species' name was available at that time, but he was talking about Bulgarian milk, and it may have been available, but it was actually referring to Bulgarian milk.

Mr. **Carter**. It was on the market as acidophilus, as I remember. Thank you, gentlemen, very much. It has been very interesting to have you here.

Mr. **Waxman**. Thank you, Dr. Carter, and I want to extend my appreciation to both of you for being here.

We will break and return at 2:15 and continue on the hearing.

[Whereupon, at 1:20 p.m., the committee recessed, to reconvene at 2:15 p.m. this same day.]

AFTER RECESS

[The subcommittee reconvened at 2:15 p.m., Hon. Henry A. Waxman, chairman, presiding.]

Mr. **Waxman**. I would like to now call the second panel of witnesses, Reuel A. Stallones, M.D., University of Texas School of Public Health; Dr. Asher Finkel, group vice president for Scientific Affairs, American Medical Association, and Dr. Joyce Lashof, assistant director, Division of Health and Life Sciences, Office of Technology Assessment.

This panel will discuss the human health effects of antibiotics resistance, what we know and what we don't know. One thing we do know from this morning, we ran much later than we expected.

I would like to make a request that those who are about to testify, if you would, if you have written statements, we will include the statement in its entirety in the record, but if you could summarize your statements in as short a period of time as possible, it would be helpful.

Let's start off with Dr. Stallones.

STATEMENTS OF REUEL A. STALLONES, M.D., ON BEHALF OF NATIONAL RESEARCH COUNCIL, NATIONAL ACADEMY OF SCIENCES; ASHER J. FINKEL, M.D., GROUP VICE PRESIDENT FOR SCIENTIFIC AFFAIRS, AMERICAN MEDICAL ASSOCIATION, ACCOMPANIED BY STEPHANIE CROCCO, PH. D., FOOD SCIENTIST, DEPARTMENT OF FOODS AND NUTRITION; AND NANCY CAHILL, DEPARTMENT OF FEDERAL LEGISLATION; AND JOYCE C. LASHOF, M.D., ASSISTANT DIRECTOR, HEALTH AND LIFE SCIENCES DIVISION, OFFICE OF TECHNOLOGY ASSESSMENT

Dr. **Stallones**. Thank you, Chairman Waxman. My name is Reuel Stallones, dean and professor of epidemiology of the School of Public Health of the University of Texas. I am very pleased to appear here on behalf of the NASNRC Committee on the effects of human health of subtherapeutic use of microbials in animal feeds, which I had the privilege to chair.

The work of this committee was supported by a contract between the Food and Drug Administration and the NRC, not, regrettably, in the amount of $1.5 million, but something like $230,000.

A summary of the report of our committee has been made available so that my remarks will indeed be supplementary and brief. I think no one disagrees with the observation that feeding antibiotics to animals leads to the development of antibiotic resistance in the bacterial species that inhabit animal intestines.

The disagreement arises over whether that phenomenon should be viewed as a hazard to human health or whether a hazard can be judged to exist only if excess human morbidity and mortality can be demonstrated to occur as a result of antibiotic feeding; that is, must the potential hazard be realized before action is taken to abate it.

Since people concerned with meat production state that banning the use of antibiotics in animal feeds will have serious economic consequences, the question requires balancing costs against benefits. The NASNRC Committee was not convened to attempt to render a judgment on that issue. Rather, our charge was to evaluate the existing epidemiological evidence bearing on the question, and suggest what further research should be done. Our study led us to conclude three primary matters.

One, human illness has not been demonstrated to occur because of subtherapeutic feeding of antibiotics to animals.

Two, the epidemiological research that relates to this issue is sparse, and often very deficient in design.

Three, a definitive study of the problem is not possible.

We were distressed to arrive at that last conclusion, but it reflects the enormous complexity of the problem. Antibiotics were widely used in human medicine, and much of the difficulty encountered with antibiotic resistance stems directly from that use. Large quantities of antibiotics are used for treatment and prophylaxis of animal diseases and to separate those from the feeding of antibiotics for growth promotion is in most circumstances not possible.

The human diseases that are of concern in this context are relatively infrequent. People obtain meat and meat products from many different sources, tracing and disentangling the transmission of antibiotic resistant bacteria from the production farms and feedlots through the processing and marketing systems into the households where the meats are consumed looks to be impossible.

During the course of this inquiry, I was told that there are three reasons why problems are referred to the National Academy of Sciences. One is that the problems are so politically sensitive that no one else will have them. Two, the problems are so boring that no one else wants them. Three, the problems are insoluble. We believe that we may have hit on all three of these.

Mr. WAXMAN. We have come across some of those here.

Dr. STALLONES. I am not surprised.

In an effort to fulfill our mission, the committee outlined four studies which would, we believe, provide useful information about some of the components of that complex system which I described, but stated that even if better data were available concerning these components, the gaps between them would still need to be bridged by inference, and hence would not resolve the argument.

We propose that a research effort devoted to explaining the mechanisms whereby antibiotic feeding promotes growth might well lead to alternatives that would be satisfactory and might render the entire issue of antibiotic feeding moot.

I realize that the report of the committee is neutral with respect to the central question. At least one person said it was about as exciting as drinking a glass of warm milk. However, our report must have had virtues which we did not anticipate when we issued it because it has received praise from proponents of both sides of the argument who apparently concluded that the report was neutral in their favor. I thank you. I will be happy to attempt to answer any questions.

Mr. **Waxman**. I am intimidated to ask any.

Thank you for your testimony and I will have some questions after we hear from Dr. Finkel and Dr. Lashof. Dr. Finkel, why don't you proceed next?

STATEMENT OF ASHER J. FINKEL, M.D.

Dr. **Finkel**. Thank you, Mr. Chairman. I am Asher J. Finkel, M.D., group vice president for scientific affairs of the American Medical Association.

Accompanying me today are Stephanie Crocco, Ph. D., food scientist in AMA Department of Foods and Nutrition, and Nancy Cahill, from AMA Department of Federal Legislation.

We have submitted for the record of this hearing a formal statement discussing these issues and my comments will briefly summarize them. [See p. 346.]

The American Medical Association is pleased to present its views on the health effects in humans resulting from the addition of antibiotics in subtherapeutic doses to animal feed and on H.R. 7285, a bill to amend the Federal Food, Drug, and Cosmetic Act to limit the antibiotic drugs that may be used in subtherapeutic doses in animal feed. We appreciate the concerns, especially the medical concerns, that gave rise to this legislation because they are our concerns as well. However, in our opinion this legislation is unnecessary. Our analysis of existing law indicates that the Food and Drug Administration, when Congress lifts its moratorium on this action, has sufficient statutory authority to curtail or prohibit the use of antibiotics in animal feed in subtherapeutic doses if indeed adequate and appropriate evidence of a public health hazard is presented.

We see two issues of medical concern. One, the growing bacterial resistance to human antibiotics and two, the toxicity of antibiotics in humans.

With regard to the first, concern was expressed in the Congressional Record of May 7, 1980, over the acknowledged problem of the growing number of bacterial strains developing resistance to human therapeutic antibiotics. Dr. Stallones has summarized the views of the National Academy of Sciences report and I need not repeat the essence of that report except to emphasize again that the report concluded that it is not possible to conduct a comprehensive and definitive epidemiological study of the effects on human health arising solely from the subtherapeutic use of antimicrobials in animal feeds largely because of the impossibility of determining the antimicrobial history of the animal from which a particular piece of meat came and the wide and varied uses of the same antimicrobials in animal husbandry and human therapy.

It is our view, however, that the movement of a disease-causing pathogen from an animal to a human population is a most unusual occurrence. Moreover, this situation is most likely to be encountered with gram-negative entero pathogens such as E. coli and various Salmonellae, where the health risk is mitigated because the bacteria have been shown to respond to a wide variety of therapeutic agents.

We are concerned, therefore, by the proposed congressional finding in H.R. 7285, that pathogenic bacteria are then transmitted to humans where they colonize and cause diseases—for which there is virtually no effective treatment. This finding does not represent the weight of the clinical evidence as to the known incidence of such transfer or the availability of antibiotic treatment.

We would also point out that clinical evidence is lacking to support the view that humans may be develolping their own resistant strains of bacteria as a result of ingesting meat or poultry that may contain a small residue of an antibiotic fed the animal during its lifetime. Nevertheless, we do believe that it is appropriate that antibiotic feeding practices cease for a sufficient period of time before slaughter to permit the animal to eliminate any residue of antibiotic, and we support the requirements of the FDA and the U.S. Department of Agriculture in this regard.

Despite our recognition of the concerns underlying H.R. 7285, however, we cannot state at this time that there is sufficient evidence of the transfer of disease-causing antibiotic resistant bacteria from animals to humans to warrant alarm by physicians or the Congress.

Again I state, at this time, with respect to the toxicity of antibiotics in humans, we seriously question whether any significant part of the current prevalence of human allergy to older antibiotics, such as penicillins and tetracyclines, can be attributed to animal feeding practices with these drugs. Accurate data indicate that any drug residue, including antibiotics, that may remain in these products is present in very small quantities—or the product is withheld from the marketplace. Although there is little clinical information regarding what happens to the residue of an animal drug in the course of human metabolism, we believe on the basis of the medical literature that the current incidence of significant antibiotic toxicity and allergy in humans is not attributable in appreciable measure to ingestion of any residue of antibiotics in animal protein.

With respect to current FDA authority, our review of existing law indicates that should it be demonstrated that current animal feeding practices using subtherapeutic doses of antibiotics present a public health hazard, FDA has sufficient statutory authority to respond. We believe that ample authority currently exists for the agency to curtail or otherwise control antibiotic use as an animal feed ingredient and as an animal drug upon a proper showing of a human health hazard. FDA's previous actions and announced policy conform to our analysis.

Any FDA action to withdraw approval of an antibiotic now approved for use in animal populations under a new evidence—regarding safety and efficacy—standard should be premised on good clinical or epidemiologic evidence. Anecdotal evidence and reports of medical oddities should not be the basis for determining risks to human health.

We believe that Congress should allow FDA to decide the issues subject to congressional oversight. We are concerned that the mandatory language in H.R. 7285 could create situations similar to those encountered as a result of the absolute language of the Delaney clause to the act that has limited FDA's ability to be flexible and to respond effectively to individual circumstances.

In conclusion, Mr. Chairman, AMA appreciates the concerns expressed in conjunction with the introduction of H.R. 7285, However, we do not believe that the weight of scientific and medical evidence supports the view that tthe therapeutic value of human antibiotics has been severely compromised or perhaps lost in the name of growth promotion by producers using small amounts of these drugs in animal feed.

The AMA does support the undertaking of the entire research program recommended in the NAS report. In the interim, it is important that the current scientific understanding of the issues under discussion here be fully and accurately ascertained and reported, and that Congress and the Federal regulatory agencies respond with policies that are based on established scientific fact.

FDA currently has authority to act to meet public health hazards and we support such actions when warranted. We urge the Congress to give FDA and USDA full support in their enforcement of existing animal drug monitoring and regulatory compliance programs.

Thank you, Mr. Chairman. We will be pleased to respond to any questions.

[Testimony resumes on p. 352.]

[Dr. Finkel's prepared statement follows:]

STATEMENT

of the

AMERICAN MEDICAL ASSOCIATION

to the

Subcommittee on Health and Environment
Committee on Interstate and Foreign Commerce
United States House of Representatives

Re: HR 7285 - "Antibiotics Preservation Act"

June 12, 1980

Mr. Chairman and Members of the Committee:

I am Asher J. Finkel, M.D., Group Vice-President for Scientific Affairs of the American Medical Association. Accompanying me today are Stephanie Crocco, Ph.D., Food Scientist in AMA's Department of Foods and Nutrition, and Nancy Cahill, from AMA's Department of Federal Legislation.

The American Medical Association is pleased to present its views on the health effects in humans resulting from the addition of antibiotics in subtherapeutic doses to animal feed and on HR 7285, a bill to amend the Federal Food, Drug, and Cosmetic Act (the Act) to limit the antibiotic drugs that may be used in subtherapeutic doses in animal feed. Our comments will principally address the perceived medical concerns that gave rise to this legislation. We appreciate these concerns. However, in our opinion this legislation is unnecessary. Our analysis of existing law indicates that the Food and Drug

Administration (FDA) now has sufficient statutory authority to curtail or prohibit the use of antibiotics in animal feed in subtherapeutic doses if indeed adequate and appropriate evidence of a public health hazard is presented.

HR 7285

HR 7285, after making several findings of a medical nature, would amend Section 507 of the Act to require FDA to "designate, by regulation, antibiotic drugs which may not be used in subtherapeutic doses...in animal feed or in ingredients of animal feed." Use of a drug that had been banned for feeding purposes under this section could be approved by FDA only if "such use is required to meet a compelling need."

MEDICAL CONCERNS

Growing Bacterial Resistance to Human Antibiotics

In the remarks published in the May 7, 1980 Congressional Record accompanying introduction of this bill, concern was expressed over th acknowledged problem of the growing number of bacterial strains developing resistance to human therapeutic antibiotics. The remarks made reference to a recently released National Academy of Sciences (NAS) report on the impact of using low levels of antibiotics in animal feeds. It is important to note that this report concluded that "it is not possible to conduct a comprehensive and definitive epidemiological study of the effects on human health arising solely from the subtherapeutic use of antimicrobials in animal feeds largely because of the impossibility of determining the antimicrobial history of the animal from which a particular piece of meat came and the wide and varied uses of the same antimicrobials in animal husbandry and human therapy" (ALS Lifelines, March 1980).

The NAS expert committee found that existing epidemiologic studies neither prove nor disprove the human hazard hypothesis. However, the committee did identify a number of factors that do contribute to the growing number of encounters with antibiotic resistant bacteria, including such causes as clinical abuses of antibiotics in humans and the incidence of nosocomial infections in human populations, and concluded that any damage that may be done as a result of using subtherapeutic amounts of human antibiotics in animal feed could not be identified or separated.

We are aware of medical and veterinary literature reporting incidents (and suspected mechanisms) of drug-resistant infection in animals spreading to a human or to a human population. It is our view, however, that the movement of a disease-causing pathogen from an animal to a human population is a most unusual occurrence. Moreover, this situation is most likely to be encountered with gram-negative entero pathogens such as E. coli and various Salmonellae, where the health risk is mitigated because the bacteria have been shown to respond to a wide variety of therapeutic agents.

We are concerned, therefore, by the proposed Congressional finding (No. 3) in HR 7285, that "pathogenic bacteria are then transmitted to humans where they colonize and cause diseases...for which there is virtually no effective treatment." This finding does not represent the weight of the clinical evidence as to the known incidence of such transfer or the availability of antibiotic treatment.

We would also point out that clinical evidence is lacking to support the view that humans may be developing their own resistant strains of bacteria as a result of ingesting meat or poultry that may contain a small residue of an antibiotic fed the animal during its lifetime. Nevertheless, we do believe that it is appropriate that antibiotic feeding practices cease for a sufficient period of time before slaughter to permit the animal to eliminate any residue of antibiotic, and we support the requirements of the FDA and the U.S. Department of Agriculture (USDA) in this regard.

Despite our recognition of the concerns underlying HR 7285, however, we cannot state at this time that there is sufficient evidence of the transfer of disease-causing antibiotic resistant bacteria from animals to humans to warrant alarm by physicians or the Congress.

Toxicity of Antibiotics in Humans

The remarks accompanying the introduction of HR 7285 also raise the concern that humans eating animal protein that may contain small residues of antibiotics are increasingly developing an allergy to, and experiencing adverse reactions to, important antibiotics, so that the use of many antibiotics in human therapeutic regimens is precluded. Particularly identified, by way of example, are penicillins and the tetracyclines.

We seriously question whether any significant part of the current prevalence of human allergy to older antibiotics, such as penicillins and tetracyclines, can be attributed to animal feeding practices with these drugs. Livestock producers and various government entities have employed accurate scientific methods for many years for the purpose of detecting any residues of drugs or other contaminants that may be in slaughtered carcasses and animal by-products. Data indicate that any drug residue, including antibiotics, that may remain in these products is present in very small quantities--or the product is withheld from the marketplace.

Though there is little clinical information regarding what happens to the residue of an animal drug in the course of human metabolism, we believe on the basis of the medical literature that the current incidence of significant antibiotic toxicity and allergy in humans is not attributable in appreciable measure to ingestion of any residue of antibiotics in animal protein.

CURRENT FDA AUTHORITY

Our review of existing law indicates that should it be demonstrated that current animal feeding practices using subtherapeutic doses of antibiotics present a public health hazard, FDA has sufficient statutory authority to respond. Under the Federal Food, Drug, and Cosmetic Act (Sections 510 and 512 and the Food Additives Amendments particularly), FDA now regulates animal drugs and substances added to animal feeds to ensure that the use of these substances does not adversely affect human health. We believe that ample authority currently exists for the agency to curtail or otherwise control antibiotic use as an animal feed ingredient and as an animal drug upon a proper showing of a human health hazard. FDA's previous actions and announced policy conform to our analysis (42 F.R. 43770).

Any FDA action to withdraw approval of an antibiotic now approved for use in animal populations under a "new evidence" (regarding safety and efficacy) standard should be premised on good clinical or epidemiologic evidence. Anecdotal evidence and reports of medical oddities should not be the basis for determining risks to human health.

We agree with the analysis of the Office of Technology Assessment in its report entitled, "Drugs in Livestock Feed, Volume I: Technical Report." That

report suggests, as one option, that Congress "allow FDA to decide the issues, subject to Congressional oversight." We are concerned that the mandatory language in HR 7285 could create situations similar to those encountered as a result of the absolute language of the Delaney Clause to the Act that has limited FDA's ability to be flexible and to respond effectively to individual circumstances.

CONCLUSION

The AMA appreciates the concerns expressed in conjunction with the introduction of HR 7285. There are significant problems today with antibiotic resistant bacteria and human allergy to the available arsenal of human therapeutic antibiotics. However, we do not believe that the weight of scientific and medical evidence supports the view that "the therapeutic value of human antibiotics has been severely compromised or perhaps lost in the name of growth promotion" (C.R., E2259) by producers using small amounts of these drugs in animal feed.

The debate on this subject is by no means closed as a result of the recent restatement by NAS of the research dilemma that exists concerning this subject. The AMA supports the undertaking of the entire research program recommended in the NAS report. In the interim, it is important that the current scientific understanding of the issues under discussion here be fully and accurately ascertained and reported, and that Congress and the federal regulatory agencies respond with policies that are based on established fact.

FDA currently has authority to act to meet public health hazards and we support such actions when warranted. We urge the Congress to give FDA and USDA full support in their enforcement of existing animal drug monitoring and regulatory compliance programs.

Mr. **Waxman**. Dr. Lashof.

STATEMENT OF JOYCE C. LASHOF, M.D.

Dr. **Lashof**. I am Dr. Joyce Lashof, Assistant Director of the Office of Technology Assessment. I am pleased to be asked to testify and to discuss the Office of Technology Assessment's report on drugs in livestock feed.

This assessment was undertaken at the request of the Senate Committee on Agriculture, Nutrition, and Forestry and completed in June 1979. The report summarizes the evidence on risks and benefits of the use of drugs in livestock feed and discusses the relevant regulatory and public policy background against which the assessment was made.

I would like to submit my full testimony for the record [see p. 355], and I am sure the committee has a copy of the full OTA report.

I have been asked today to restrict my comments to the specific question of the effect on human health and I would like to just make a couple of points.

Dr. O'Brien and Dr. Savage I think this morning amply explained the mechanism of transfer of antibiotic resistance from the use of antibiotics generally, be they subtherapeutics in animal feed or be they in the treatment of human disease.

They further discussed the plasmid mediated resistance problem and the fact that resistance can be transmitted from one bacterium to another, and that this presents the potential danger to human health.

I guess the real policy issue before this committee is what evidence does the policymaker need before deciding on potential risks, and how does he balance those risks against the benefits?

If we look at the issue of what is the evidence, what kind of evidence could we be looking for, well, there are three types of evidence one could look for.

One is evidence that animal feed uses are contributing to the general pool of drug-resistant bacteria. The second type is illness in handlers of food animals with the illness shown to be a result of bacteria made resistant by the use of antibiotics in animal feed.

The third would be illness in other than the direct handlers of food animals with the evidence to show that the illness stemmed from bacteria made resistant to antibiotics directly or indirectly through the use of those antibiotics in animal feed.

Now, most studies on this subject have concluded that the evidence in the first category, that is that the use of antibiotics in animal feed does increase the pool of genetically drug-resistant bacteria has been shown, and many consider that a serious risk in itself, although that cannot be quantified.

The second category, that of illness in food handlers, has been shown through occasional outbreak of disease in food animal handlers. There is also ample evidence that the drug-resistant bacteria are transferred from the food animals and colonize the intestinal tracts of the food animal handlers and their immediate contacts.

It is the third category of risks, showing a direct causal relationship between the specific use of antibiotics in food animals to illness in other than food handlers that would be the most convincing evidence of human risk.

This, however, requires tracing specific bacteria made resistant by the use of antibiotics in animal feed that are consumed by specific food animals through the food processing chain or through the transfer between humans and then proving that that particular bacterium was the cause of recognizable disease in those humans.

The recent report of the National Academy of Sciences chose this latter definition of human risk, but concluded that it could not be shown; that the causal chain could not be proven.

They also stated, however, that the causal chain could not be disproven.

Our conclusion was that the increasing pool of resistant bacteria is a serious health risk to humans, and that the contribution from low-level antibacterial use in animal feeds played a significant part in increasing the general pool of genetically resistant organisms.

The identification of plasmids and the identification of the ability of the plasmids to move from one bacterial species to another was the overriding evidence for our position.

Further, although the complete causal chain required by category 3 had not been proven or disproven, each of the links in the chain has been demonstrated.

We also pointed out that it was not relevant that the therapeutic use in humans of these same antibacterials may be a larger contributor to the development of resistance, as long as animal feed use was in itself a significant contributor to resistance.

In policy terms, it is not helpful, only distracting, to point to a potentially larger contributor to the problem to determine what should be done.

Furthermore, at any point in time the number of animals exposed to antibiotics far exceeds the number of humans exposed, and the length of therapy in humans averages less than 10 days, while antibiotic supplemented animal feed use is often continuous.

The question of which standard of proof should be taken is of obvious relevance to the public policy and regulatory processes.

Actual use of what constitutes a serious risk to human health, that is, the genetic pool of drug-resistant bacteria, is consistent with the predictive value of science in helping to determine public policy.

To the extent practical, the regulatory process in the human health area has been concerned with preventing significant risk from occurring. This is most obvious in the area of cancer-causing agents, where primary reliance is on the predictive power of animal testing and other laboratory procedures. Human epidemiology studies, of course, are the best evidence of human health effects, but what they prove is that the risks that we are trying to avoid have already occurred. Thus direct evidence of human disease confirms the experimental evidence and helps to quantify the magnitude of the problem.

However, public policy in regulating risks to human health has not relied on direct human studies for the primary evidence of risk, and we do not expect this outlook to change as long as prevention remains the primary approach.

The final decision as to whether or not a potential health risk should be accepted or not will depend upon whether or not one believes the benefit of whatever thing it is that is causing the risk outweighs the potential risk and I think that is the issue before this committee.

[Testimony resumes on p. 363.]

[Dr. Lashof's prepared statement follows:]

STATEMENT OF

JOYCE C. LASHOF, M.D., ASSISTANT DIRECTOR

OFFICE OF TECHNOLOGY ASSESSMENT

I am Dr. Joyce C. Lashof, Assistant Director of the Office of Technology Assessment. I am pleased to be asked to testify and to discuss the Office of Technology Assessment's report on Drugs in Livestock Feed. This assessment was undertaken at the request of the Senate Committee on Agriculture, Nutrition, and Forestry and completed in June 1979. The report summarizes the evidence on risks and benefits of the use of drugs in livestock feed and discusses the relevant regulatory and public policy background against which the assessment was made.

Drugs are used in the rearing of animals for human consumption for five reasons:

1. As nutritional supplementation, such as when vitamins and minerals are given;
2. For treating disease;
3. For preventing disease;
4. For increasing weight gain;
5. For improving feed efficiency.

As the use of drugs in animal feeds either as nutritional supplements or for therapeutic purposes is relatively non-controversial, the report focused on the addition of low levels of antibacterials to feeds and on diethylstilbestrol (DES), a synthetic estrogenic hormone which is a proven human carcinogen. Since the release of our report, this use of DES has been banned. I will therefore only summarize that part of the report that deals with the use of antibacterials in livestock feed and the relevant public policy issues.

More than 40 percent of the antibacterials produced in the United States are used as animal feed additives and for other non-human purposes. Nearly 100 percent of poultry, 90 percent of swine and veal calves, and 60 percent of cattle receive antibacterial feed supplementation.

This widespread use of antibacterials has led to increasing concern over potential adverse effects on human health because many of the same antibacterials are used both in human therapy and in animal feeds. The use of these drugs as feed additives contributes to a growing pool of drug-resistant bacteria. Physicians are now reporting reduced effectiveness of these same drugs in treating human disease. Some bacteria are resistant to several antibacterials; others require higher doses to control or kill them. Research findings point to animal feeds as a contributory source of many of these drug-resistant bacteria.

There is much disagreement among scientists as to the validity of many of the findings and the weight that should be attributed to them when considering a ban or restrictions on the use of these drugs. The two main areas of dispute are:

1. What the effects are on human morbidity and mortality,
2. What tradeoffs there should properly be between risks and benefits.

The risks from the use of antibacterials in animal feeds stem from an increase in bacterial resistance to the drugs. Drug-sensitive bacteria are killed or inhibited by the drug, allowing resistant bacteria, which have adapted to the presence of the drug, to grow in their place. While drug-resistant variants exist even in the absence of antibacterials, they do not generally flourish unless a change in their environment favors their survival. When antibacterials are given, the drug-resistant bacteria are the fittest to survive in their presence, and they soon become the majority.

Genes for antibacterial resistance as well as its transfer are carried on structures called plasmids, which are bits of DNA that function independently of the organism's main genetic apparatus. Plasmids can transfer resistance between bacteria of the same or of different species. Thus, harmless resident bacteria, such as E. coli, which are present in the intestines of humans and animals, can become resistant in the presence of the drugs and can then transfer their resistance to a still sensitive strain of a more virulent pathogen such as Salmonella. The result of such a transfer would be a strain of Salmonella that was resistant to one or more antibacterials. The resident bacteria in the intestines of animals and humans receiving antibacterials are soon replaced with resistant resident bacteria and thus serve as a reservoir for the spread of plasmid-mediated resistance to antibacterials.

While research attention was originally focused on the transfer of drug resistance from E. coli to other intestinal microorganisms, principally Salmonella, it is now evident that the spread is wider. There is now strong evidence that similar transfers occur between H. influenza and N. gonorrhea and resistant E. coli. Thus, the risks are no longer restricted to people who may have picked up Salmonella directly from animals or their edible products.

N. gonorrhea and H. influenza are harbored by humans. For these bacteria to have acquired plasmids for the transfer of resistance means that the plasmids are traveling in a wider radius than was originally predicted. For instance, identical plasmids have been isolated in parts of the world as distant as England and Vietnam.

Furthermore, plasmids are now carrying genes for resistance to more than one drug. Whereas formerly this was rare, it is now common, if not usual, for bacteria to be resistant to several drugs at a time. It is now necessary for physicians to run sensitivity tests to determine alternative drugs to which a given strain of bacteria is still sensitive. Certain strains of gonorrhea and typhoid, among others, have proven more difficult to treat than formerly as a result of resistance to the standard drug of choice.

The extent of the decrement in performance of antibacterials used in treating human and animal disease is still relatively unknown. The relationship between decreased sensitivity and decreased effectiveness in treating disease is complicated because many variables such as species, general health, and numbers of invading bacteria influence whether known pathogenic bacteria will cause observable disease and whether a specific drug will make the difference in outcome when disease does occur. This is particularly true for Salmonella, the bacteria on which much attention has been focused. However FDA estimated that in 27 percent of the Salmonella cases treated each year, the first antibacterial chosen for treatment proved to be ineffective because the disease was caused by antibacterial-resistant bacteria.

Another risk from the use of antibacterial feed additives is that it eventually compromises therapeutic and prophylactic effects of the same drugs. Even though stopping the use of an antibacterial can be expected to result in the loss of dominance of resistant bacterial strains, these strains can persist in diminished but significant numbers. If growth promotion and feed efficiency are closely dependent on disease prevention, the effectiveness of supplemental antibacterial feeding will decline.

While the contribution to the pool of drug-resistance bacteria from the use of antibacterials in animal feeds is not in dispute, the cause-and-effect relationship between such uses and human disease _is_ in dispute. Proof of risks to humans can be roughly categorized into:

1. Evidence that animal feed uses are contributing to the general pool of drug-resistant bacteria.
2. Illness in handlers of food animals, with the illness shown to be a result of bacteria made resistant by the use of antibacterials in animal feed.
3. Illness in other than the direct handlers of food animals, with evidence to show that the illness stemmed from bacteria made resistant to antibacterials, directly or indirectly, through the use of antibacterials in animal feed.

Most studies on this subject have concluded that the evidence on the first category, an increased pool of drug-resistant bacteria, has been shown and constitutes a serious, although non-quantifiable, risk. The second category has been shown through occasional outbreaks of disease in food animal handlers. There is also ample evidence that drug-resistant bacteria are transferred from the food animals and colonize the intestinal tracts of food animal handlers and their immediate contacts. The third category of risk, showing a direct causal relationship between the specific use of antibacterials in food animals, would be the most convincing evidence of human risk, but it requires tracing specific bacteria -- made resistant by the use of antibacterials in animal feeds that are consumed by specific food animals -- through the food processing chain or through transfer between humans, and then proving that such bacteria cause recognizable disease in those humans.

The recent report of the National Academy of Sciences chose this latter definition of human risk, but also concluded that the causal chain could not be proven. Our conclusion was that the increasing pool of resistant bacteria is a serious health risk to humans and that the contribution from low level antibacterial use in animal feeds played a significant part in increasing the genetic pool of resistant organisms. Further, although the complete causal chain required by category three has not been proven or disproven, each of the links in the chain has been demonstrated.

We also pointed out that it was not relevant that the therapeutic use in humans of these same antibacterials may be a larger contributor to the development of resistance, as long as animal feed use was in itself a significant contributor to resistance. In policy terms, it is not helpful, only distracting, to point to a potentially larger contributor to the problem to determine what should be done. Furthermore, at any point in time, the number of animals exposed to antibacterials far exceeds the number of humans exposed, and the length of therapy in humans averages less than 10 days, while antibacterial-supplemented animal feed use is often continuous.

The question of which standard of proof should be taken is of obvious relevance to the public policy and regulatory processes. Our choice of what constitutes a serious risk to human health -- i.e., the genetic pool of drug-resistant bacteria -- is consistent with the predictive value of science in helping to determine public policy. To the extent practical, the regulatory process in the health area has been concerned with preventing significant risks from occurring. This is most obvious in the area of cancer-causing agents, where primary reliance is on the predictive power of animal testing and other laboratory procedures. Human epidemiology studies, of course, are the best evidence of human health effects, but what they prove is that the risks that we are trying to avoid have already occurred. Thus, direct evidence of human disease confirms the experimental evidence and helps to quantify the magnitude of the problem. However, public policy in regulating risks to human health has not relied on direct human studies for the primary evidence of risk, and we do not expect this outlook to change as long as prevention remains the primary approach.

Our study also examined the evidence on the benefits of the use of drugs in animal feeds. Most of the attention has been focused on the risks of such uses, and the scientific evidence on risks has been very closely examined. We want to point out that the scientific evidence on benefits is dated, and, if subject to the careful examination given the risk data, would be severely criticized. We also recognize, however, that these uses have been in practice for several decades and are integral to the production methods of large producers, and that it is much more difficult to question the effectiveness of something already on the market than it is to question the effectiveness of a new product which has not yet been approved for use.

Assuming that the increased production attributable to antibacterial-supplemented feeds is real and of the magnitude predicted by the experimental evidence, our report summarized two studies on the economic effects of taking certain antibacterials off the feed supplement market. These analyses assumed that selected antibacterials were simply banned, with no substitutes available. The findings were that production would be decreased in the period immediately following a ban; higher prices would offset the decrease in quantity and lead to higher consumer prices but also to higher producer incomes; and that the long-term consequences (i.e., by the fifth year) were little or no change in the quantity of food animals produced and small increases in both consumer prices and overall producer incomes. These economic analyses might be viewed as "worse case" scenarios, as there are substitute antibacterials already approved.

What is the tradeoff between such economic benefits and the risks to health? The lack of scientific certainty on the magnitude of both the health risks and the increases in meat production make formulation of a balance-sheet approach difficult. These decisions involve value judgments that cannot be based simply on monetary considerations. But scientists and policy analysts can help to clarify the issues underlying this question. The Office of Technology Assessment has concluded that the health risk should be defined primarily as the contribution of antibacterial-supplemented feeds to the growing genetic pool of bacterial resistance. We see more direct evidence of human illness as confirmatory evidence. In our opinion, this is the approach that should be taken — and which is taken in assessments of health risks in other public policy areas such as food additives and environmental contaminants — as long as we are primarily concerned with preventing health risks, instead of waiting until after-the-fact and taking ameliorative actions as our primary approach to these problems.

Mr. **Waxman.** Thank you very much.

Dr. Stallones, you just heard Dr. Lashof's report and maybe you had the opportunity to read the Office of Technology Assessment's report. Do you subscribe to the theory that the general pool of drug resistant bacteria is increased because of the use of antibiotics among animals?

Dr. **Stallones.** Yes, sir.

Mr. **Waxman.** How about you, Dr. Finkel? Do you subscribe to that theory also?

Dr. **Finkel.** Yes, there is no question that it has been increased. The question is where has it been increased, in what population.

Mr. **Waxman.** Is it largely in the animal population or has it spread over significantly into the human population?

Dr. **Finkel.** I think that is the significant problem.

Mr. **Waxman.** Do you accept the premise that bacteria moves between animals and human beings to some extent, and that there is not a static pool of bacteria only for animals as opposed to a static pool of bacteria in humans?

Dr. **Finkel.** Yes, of course, the bacteria move to some extent. The question is also the extent of the extent, if I may phrase it that way.

Mr. **Waxman.** If we are adding to this general pool of drug resistant bacteria to which humans may then find ourselves exposed, wouldn't it be prudent, Dr. Stallones, for us to try to limit the impact on that overall pool of drug resistant bacteria insofar as we could?

Dr. **Stallones.** Yes, sir. Our committee would, I am sure, unanimously believe that that would be a good thing to do. The question exists as to whether the limitation proposed would accomplish that end. The data with respect to that are not strong, but they do not support the notion that good effects do happen in those places where the use of antibiotics for feeding has been banned.

Mr. **Waxman.** Let me ask a question that is probably more relevant, and Dr. Finkel is probably the one to ask this question. We do know that if there is an excessive use of antibiotics that it does create a pool of drug resistant bacteria in people.

Do you think that there is a problem from excessive use of antibiotics by their patients?

Dr. **Finkel.** I think the pool of antibiotic resistant bacteria in the human population is probably in large part due to the administration of antibiotics to humans. Whether that is an appropriate use of antibiotics in each individual case is a separate question.

Mr. **Waxman.** Yes.

Dr. **Finkel.** But undoubtedly the growth of resistance on the part of human bacteria is due largely to the fact that they have been exposed in humans to these new compounds.

Mr. **Waxman.** From just your general knowledge in an overall sense, without commenting on the specific use of antibiotics with an individual patient, do you feel that there is excessive use of antibiotics with human beings that may be unnecessary?

Dr. **Finkel.** That is a very difficult question to answer. It may very well be that in some cases more antibiotic is prescribed than is warranted medically. On the other hand, when one evaluates individual patients, the cases may be quite different. It is very difficult to speak in generalized terms.

Mr. Waxman. What would be your opinion of long-term use of a low potency antibiotic by a dermatologist for acne? Do you think that is a prudent approach, where we do have a potential problem to the overall pool of drug resistant bacteria?

Dr. Finkel. Well, from the point of view of society, it may be imprudent. From the point of view of the youngster or young adult who has severe acne, there are different values and different criteria that may apply.

We are dealing with a very complex situation and it is a little difficult to apply societal rules to individuals and individual rules to society. There are very real problems, though, no question about it.

Mr. Waxman. We heard earlier from Dr. Savage, who felt that the legislation that is before us does not address that particular problem which he sees as a real problem, not that he had a recommendation to us to do anything about it legislatively one way or the other, but pointed out that if we looked at animal feed antibiotic use, that we might well think that there is no problem in other areas of exposure to antibiotics. I am wondering whether we can say that for an individual for cosmetic purposes only the use of an antibiotic can be justified, if there is a detrimental impact on the pool of drug resistant bacteria overall.

Dr. Finkel. I think that is a very valid point. I think these things have to be weighed.

Mr. Waxman. Dr. Lashof, you have come down to the point where balancing the risks and benefits without that clear causal nexus being established that for public health purposes it would be far more prudent to limit the use of antibiotics in animals.

Dr. Lashof. Yes, I think that is because what I didn't go into here but we do go into, of course in the report, is the evaluation of the benefits and what harm would be done, and what the impact of limiting penicillin and tetracycline would be, and if I can summarize those briefly, because, as I have said, the principal issue is the balance and you can't be absolute without having looked at both sides of the equation.

Mr. Waxman. Please summarize.

Dr. Lashof. The report indicates that the data on the benefits from the use of animal feed are subject to about the same criticisms that have been leveled against the data on the risks.

The data is not absolute one way or the other. However, they have been used for a long, long time, and to try to do an experiment to try to prove how useful it would be is extremely difficult, as difficult as some of the human epidemiologic studies are.

However, there were two studies done on what the economic impact would be of now removing antibiotics from animal feed, one done by USDA and one done by an economist named Hedley.

Now, in both of those studies the assumption was that there were no substitutes available. Both of the studies showed immediate economic impact which disappeared over time. It was either USDA—one had it disappearing over a shorter period of time, one over a longer period of time. However, when both were asked the questions now looking at the substitutes, it appears there would be very little economic impact if substitutes were available, and since what is being proposed is that use be restricted to where substitutes are available, it is hard to see what would be the harm done by restricting. And since then we have the potential benefit of decreasing a major contributory factor to the risk, we would come down that under those circumstances the prudent policy decision would weigh towards the direction of restricting where substitutes were available as being the logical conclusion.

Mr. **Waxman**. Dr. Finkel, you indicated you thought FDA already had the power to act, should more evidence be established which would indicate that they ought to act. Under what circumstances would you think FDA might act in dealing with this problem of antibiotics in animal feed?

Dr. **Finkel**. If there is clear evidence of a danger or hazard I think that FDA has the responsibility to act.

Mr. **Waxman**. Do you think that we can ever get clear evidence of the danger from what you have seen of the scientific work?

The National Academy of Science has done its study, and they claim that epidemiological evidence is insufficient; that it is not feasible to study this problem to reach a clear enough conclusion.

Dr. **Finkel**. The National Academy report recommended a number of studies that would throw more light on the problem. If those studies should in fact be done, and do give evidence of a substantial danger, then I think the FDA has the responsibility to act accordingly.

Mr. **Waxman**. Let me ask Dr. Stallones what the National Academy of Sciences thinks might be done to further study the issue to help us make some determination about it?

Dr. **Stallones**. We judged that among the important questions that had not been resolved, is the incremental burden of antibiotic resistant enteric bacteria that results directly from the use of antibiotics in feeds, and we thought the only way that could be addressed was not in an epidemiological study but in an animal experimental study in which animals would be subject to the kind of animal husbandry practices which were customary, but under carefully observed and controlled conditions, so that one could indeed assess whether animals given that amount of therapeutic antibiotics which would usually occur during the course of raising animals would result in a different burden of antibiotic resistance than would occur with feeding.

It was our understanding that in some circumstances whether antibiotics are fed for growth promotion or not, nearly all animals in some settings receive antibiotics.

The next issue which we thought should be addressed more quantitatively is the risk to animal handlers. I think myself that the evidence that Dr. Lashof referred to is not as strong as I would wish. The numbers of studied subjects in those studies have been very small, too small to establish very significant differences between the observed groups. We think that it would be medium expensive, but it is probably well worth while to establish clearly what the risk of transfer of organisms from animals to animal handlers and to slaughterhouse workers, and to observe the workers long enough to answer some of the questions that relate to the duration of colonization with the animal strain. To attempt to pursue that further in order to ascertain whether or not illness occurs that is directly attributable to antibiotic resistant strains derived from feeding antibiotics is probably not financially feasible. The risk of disease is low enough so that in order to collect enough cases one would have to have enormous populations of animal handlers and slaughterhouse workers available, follow them over very considerable periods of time, and it doesn't seem likely.

One other kind of study that has been done in a small way in the past is to compare people who eat meat with people who do not and attempt to assess any quantitative difference in the nature of their enteric bacteria which looked interesting. We thought there are large enough populations so that that would well be worth pursuing.

Without speaking directly for the committee—oh, there was one study that attempted to address disease directly, but I think it would be extraordinarily difficult to derive very much use from that. It had to do with urinary tract infections with *E. coli,* and I think would be a difficult study.

The extra comment is very brief. It was mentioned during the course of our committee discussions, but does not appear in the committee report. Really there are only two diseases that deserve very much consideration as being directly attributable to antibiotic and I think these are *E. coli* urinary tract infections and salmonellosis; with respect to the former, as I said, it is very difficult to study. We had on the committee Dr. Kass who is one of the world's experts in this field and he was not very enamored of trying to pursue this further.

With respect to salmonellosis derived from animals—we are not talking about typhoid fever, but the food poisoning *Salmonella* infections, the problem of salmonellosis will still be there and from a public health point of view that is a preventable disease.

Whether or not legislation is passed banning the use of antibiotics in animal feeds, we would be delighted to see additional efforts placed on preventing *Salmonella* infections. Whether the *Salmonella* are antibiotic resistant or not, they are still there, so this legislation would have no effect on the frequency of salmonellosis in this country, and that could be attacked. It is a public health argument.

Mr. WAXMAN. Let me ask this of Dr. Stallones and Dr. Finkel. Let me ask you another question first, Dr. Stallones. Did the National Academy of Sciences look at the loss to industry by use of an alternative, or were you looking solely at the detrimental impact on humans, if any?

Dr. STALLONES. There has been a fair amount of misunderstanding, I think, of the charge that the committee had, and we did not look at the cost of banning antibiotics. We obtained some information about that, but it was not relevant to our charge, and our charge was indeed limited to presenting recommendations with respect to additional epidemiological research that should be done to cast light on the issue.

In order to make that judgment, we reviewed the epidemiologic literature quite carefully and it is on that basis that we judge it to be deficient.

Mr. **Waxman**. The question to each of you gentlemen: You both take the position that we ought not to adopt legislation; that we don't have sufficient evidence to reach the conclusions that would justify the U.S. Congress passing a law that would ban subtherapeutic use of antibiotics in animals.

If each of you, however, had been called in as a consultant by someone who was the head of an industry group, a person involved in cattle, poultry, and this person was particularly civic minded and said to each of you:

> Well, you have studied this issue. I know you don't think the Congress ought to tell us what to do, but if I wanted to do what was right for society generally and be prudent about it, would you recommend that I use an alternative, if an alternative is generally as good?

Dr. Finkel.

Dr. **Finkel**. Mr. Chairman, I don't think I would allow myself to be a consultant to the cattle industry. That is a very difficult question. I think that any advice that I personally would give would have to be based on my evaluation of what the scientific literature showed.

At this point, I personally am not convinced that there is a clear and imminent danger. I am quite willing to change my mind if more information is forthcoming.

Mr. **Waxman**. Dr. Stallones?

Dr. **Stallones**. Well, I think it is not a difficult question to answer. I would like to state that I am not arguing against the legislation. The only argument that Dr. Lashof and I have at all—well, I think we have no argument at all.

If one judges that inducing antibiotic resistant organisms in animals is a human health hazard, then one would support the legislation.

If one judges that one must know that this produces human illnesses, then I say we do not know that this produces human illness.

With respect to my advice, I would charge a very high consultation fee.

Mr. **Waxman**. There is no question I couldn't afford you.

Dr. **Stallones**. And I would advise them to use an alternative.

Mr. **Waxman**. Immediately I would fire you.

Dr. **Stallones**. If it were available but I would already have collected. This is a very civic-minded producer, and I think for all kinds of reasons his cause would be furthered if he got out of that zone of action.

As a matter of fact, he could use it in his advertising campaigns and run his competitors into the ground.

Mr. **Waxman**. Thank you. Of course, I was joking for the record when I said I would fire you.

Dr. Finkel, do you think that physicians are aware that there may be a potential danger to the human pool of bacteria resistance by use of antibiotics, and that they might keep that in mind when they use antibiotics as they consider the general overall good compared to the individual therapy and balance those?

Dr. **Finkel**. I think there is an increasing awareness on the part of physicians of the larger dangers of the use of antibiotics, the consequences. I think there is a whole new generation of physicians that has been trained in much more modern medicine than the physicians that were practicing at the time these antibiotics first came into use, and I think there is a growing awareness of the problem of appropriate prescribing, the problems of unnecessary prescribing, and also the problems of patient compliance. Patients frequently will not comply adequately when they are given oral doses especially of antibiotics.

I think there is also an increasing awareness on the part of the profession. I wouldn't want to say that every physician in the country practices appropriately, but I think that the quality is improving all the time.

Mr. WAXMAN. You are here representing the American Medical Association, are you?

Dr. FINKEL. Yes, sir.

Mr. WAXMAN. Are you aware of activities by the American Medical Association that would increase that awareness among physicians?

Dr. FINKEL. Yes, I am. We put out a very important compendium of advice for physicians on the use of drugs called *AMA Drug Evaluations*, and a large portion of that book is devoted to the various antibiotics.

This book is revised every 3 years and we urge physicians to use it extensively in the hopes that they will improve the scientific basis of their practice.

Mr. WAXMAN. I am pleased to hear that, and I want to commend the AMA for taking that action, because I think that so much of what we are asked to do here in Congress can be taken care of through voluntary action, by the medical community in the case of unnecessary or over-exposure to antibiotics, and perhaps by the agricultural community, so to speak, in looking to move to alternatives just as a more prudent way of living up to what may be societal good.

Dr. Carter, do you want to give them a real rigorous examination on the science involved? These are scientists who can answer your questions.

Mr. CARTER. I don't want to do that but I might ask them a few questions.

Mr. WAXMAN. I will recognize you for that purpose.

Mr. CARTER. Thank you, Mr. Chairman.

A while ago I forgot the four benzene rings which are included in tetracycline and I put them up there just now. If instead of an oxiradical we placed chlorin on one, what would it have been?

Dr. FINKEL. It would have been one of the congeners in the family of the tetracyclines.

Mr. CARTER. It would be aureomycin, I believe, is that correct, Dr. Lashof?

Dr. LASHOF. I have been a policymaker too long.

Mr. CARTER. You both are experts in this field. I am not. I am an old country doctor, way back in the hills. I am not supposed to know that.

Mr. WAXMAN. You can be sure that the city slicker lawyer who is your chairman doesn't know it.

Mr. **Carter**. Of course, the sulphanilamides were first developed about 1935, 1936, or 1937. Has there been resistance of bacteria developed to the sulphanilamides over the years, Dr. Finkel?

Dr. **Finkel**. I believe there has.

Mr. **Carter**. Yes, sir, there has been. Has there been a medicine to which resistance has not to some extent occurred from the many medicines that you know of, Doctor?

Dr. **Finkel**. I am doing a quick mental review of pharmacology. I think that some of the chemical substances that are direct poisons in large part are too toxic to allow the development of resistance.

Mr. **Carter**. Probably salvocyllin or the other mercurials.

Dr. **Finkel**. There is development of resistance to various arsenicals.

Mr. **Carter**. In almost every medicine, every antibiotic certainly, there has been a development to where the medicine simply would not take effect.

In the case of penicillin, can you tell us about when the resistance to penicillin developed by some bacteria, gonorrhea, the gonococcus was the first I believe that we noticed. Do you remember about when that was first noted?

Dr. **Finkel**. It was in the late forties.

Mr. **Carter**. Sir?

Dr. **Finkel**. In the late forties.

Mr. **Carter**. In the late forties. I believe you are correct, sir. In this case it is a little bit farfetched in my opinion, and we really don't know that this resistance would be transmitted to humans from the animals, is that correct or not, bacteria that had become resistant to penicillin or tetracycline, then invaded the human system.

Would there be necessarily an inability of the human body to cope with it or not?

Dr. **Finkel**. No, the natural immune mechanisms would certainly assist the human body in coping with pathogenic bacteria.

Mr. **Carter**. It would do that. There are so many others. I differ with some about the development of new medicines. For instance, in the field of antibiotics, instead of giving four 250 milligram tablets of terramycin a day now we use vibramycin quite often and we have a beginning dose usually of two capsules a day and after that one. Is that about correct, Dr. Lashof?

Dr. **Finkel**. For vibramycin?

Mr. **Carter**. Yes.

Dr. **Finkel**. Yes, sir, that is the usual dose.

Mr. **Carter**. The usual dose, but sooner or later—sometimes we get two a day, but it is a pretty potent antibiotic, but sooner or later why there will be strains that will become resistant to that, is that not correct?

Dr. **Lashof**. Very likely.

Mr. **Carter**. I would think so.

By the way, what is the treatment of choice in the case of *ebrethellatiphosa* (sic) infection?

Mr. **Waxman**. Two aspirin.

Dr. **Finkel**. Chloramphenicol.

Mr. **Carter**. That is correct. What is the most dangerous drug now to humans that is used, that causes more deaths per year than any other, I mean in the antibiotic field.

Dr. **Finkel**. Penicillin.

Mr. **Carter**. Yes, sir, absolutely.

That is something that few people realize. We have discussed chloramphenicol over the years. What is the average rate of death from that?

Dr. **Lashof**. In terms of the percentage of people that were given it?

Mr. **Carter**. Yes, ma'am, the percentage. Who received it and who died as a result of it?

One in 40,000 according to the last statistics that I received. Causes leukopenia as I recall, is that correct?

Dr. **Finkel**. Yes, sir, I believe it is.

Mr. **Carter**. The bone marrow no longer produces the cells. Dr. Weiss, I see you shaking your head. Am I wrong?

Dr. **Weiss**. No, sir.

Mr. **Carter**. Dr. Weiss was formerly a professor at the University of Kentucky and is now a member of the National Academy of Sciences, and I wanted to introduce him as a fellow Kentuckian. It has been a pleasure talking with you people. It always is.

I believe we have a division of opinion, but I really think that we should know or have a firm basis on which to proceed before we legislate. What about that, Dr. Lashof?

Dr. **Lashof**. Well, yes, obviously I think we should have a firm basis. I think, as I indicated, and I guess you were not here for my testimony——

Mr. **Carter**. I got the drift.

Dr. **Lashof**. That the potential of a risk I think is something that must be weighed against the potential of the benefit, and when something is extremely beneficial, then the evidence for the risk I think must be greater before one acts, while when the benefits are minimal, then a potential risk may be sufficient to act and it is this kind of equation——

Mr. **Carter**. What direct proof do we have of these dangers which are projected?

Dr. **Lashof**. Well, I think I depend on science to teach us something about the mechanisms, and I think if I would make two points, they really are related to the testimony we heard this morning from Dr. Savage and Dr. O'Brien, and to clear this up I think the issue is not whether there are antibiotics in food and whether we eat the food with the antibiotics and that then does something to the bacteria in our gut, nor is it even a simple problem that we produce antibiotic resistant organisms in animals, and then those organisms are directly transferred to man. I think issue is the the understanding of science in the new contributions of the identification of plasmids, and the fact that this genetic material can be transferred from one bacterium to another, so that bacteria which have become resistant by being exposed to antibiotics in the animals, that these bacteria then get into the general environmental pool of bacteria, and by the fact that there appears to be little compartmentalization at least at that level, that those plasmids get transferred from one bacterium to the other; that the potential then exists that a significant amount of resistant organisms we see in human beings were indeed induced by that kind of mechanism.

Now, this is impossible to prove in any specific case. There is no question but science is a predictive science, and it is the prediction and the theory of science in which I think we have to weigh.

Mr. **CARTER.** This is a hypothesis, isn't it? Science really is based on fact and not projection.

Dr. **LASHOF.** The plasmids aren't hypothesis, and the transfer of resistance by plasmids is not hypothesis. That is hard scientific data, as I understand the literature.

Mr. **CARTER.** This same sort of thing got us into the swine flu vaccine epidemic. By the way, did you testify on that too?

Dr. **LASHOF.** No, I didn't, Mr. Carter. I was a State health officer injecting everybody in the State of Illinois at that time.

Mr. **CARTER.** I was one of those who supported that on the basis of scientific evidence. I thought having heard from the world's leading scientists, and it resulted in hundreds of cases of Guillain-Barré syndrome, I believe. Thank you very kindly. It has been very interesting.

Dr. **LASHOF.** Thank you very much.

Mr. **WAXMAN.** Thank you, Dr. Carter, and we thank each of the witnesses.

Just as an observation, it occurs to me we ought to have battle pay for the court reporters in a hearing like this.

Let me now call forward the third and last panel.

Eugene I. Lambert, Covington & Burling, representing the Animal Health Institute.

William L. Hewitt, chief, Division of Infectious Diseases, Department of Medicine, UCLA.

George T. Edds, D.V.M., professor of veterinary medicine and toxicology, University of Florida

William J. Visek, M.D., School of Basic Medical Sciences, University of Illinois, representing the American Society for Animal Sciences.

Mr. **WAXMAN.** Dr. Edds, I am going to recognize you first, based on my understanding of whose flight leaves first.

STATEMENTS OF GEORGE T. EDDS, D.V.M., PH. D., PROFESSOR OF VETERINARY MEDICINE AND TOXICOLOGY, UNIVERSITY OF FLORIDA; WILLARD J. VISEK, M.D., PH. D., ON BEHALF OF AMERICAN SOCIETY FOR ANIMAL SCIENCES; WILLIAM L. HEWITT, M.D., DIVISION OF INFECTIOUS DISEASES, DEPARTMENT OF MEDICINE, SCHOOL OF MEDICINE, UCLA; AND EUGENE LAMBERT, COUNSEL, ANIMAL HEALTH INSTITUTE

Dr. **EDDS.** Mr. Chairman, I would say as others have said today that have been invited to appear before your committee, that I have enjoyed this opportunity of being here, so that I can benefit by the experience that others have had, and also hope to share some of the experiences that we have had there as far as since I am a veterinarian, looking at the animal health aspects and ultimately the human health potential hazard as far as the use of antibiotics.

We know from history that the antibiotics were first introduced about 1950 as animal feeds, and in the sense that there was a factor present, the animal protein factor (APF), we didn't know what it was at the time; it was later found that that was vitamin B_{12} one of the essential vitamins, and so along with the introduction of these animal protein factors, vitamin B_{12} there were also antibiotic residues, and the antibiotic residues did show when they were included in the animal feeds as used on the farm for cattle, swine, and poultry, that growth performance was improved.

Feed efficiency was improved, so they gained a foothold or they were established because of this observation that there was improved animal health.

Now, it is difficult, as has been pointed out today, to define animal health. What is a healthy animal? What is a healthy person, and so the few comments that I would like to make, I have a copy of a paper here on adverse drug effects and several of the speakers today have alluded to this [see p. 375], that actually the exposure of humans to antibiotics may be a greater predisposing factor than this low level of antibiotics present in the feed as a residue problem.

I think my experience working with the people in the Veterinary Division, Food and Drug Administration, the feed section of the BVM, is that when a problem has been pointed out to them, they have done an effective job in communicating this problem to the public, acquainting the public with this hazard, and helping reduce the hazard, and I will use a specific example.

At the time that the mastitis products were being popularized as effective treatment for bovine mastitis, I was in industry at the time and several of the other industries as well as our own were guilty of the fact of increasing the antibiotic level in the mastitis treatments to an inordinate level, too high, and because of that we had the presence of antibiotics appearing in the milk. Several of the speakers today have alluded to the fact that the penicillin is a highly sensitizing antibiotic. At that time, we recognized that the way to reduce this hazard was to reduce the dosage level that was being used in the individual animal in the quarter to treat the mastitis. With the performance by the people in Food and Drug Administration, as well as through the veterinary profession and the dairy industry, this hazard was markedly reduced.

I have seen reference in the last year or so in which the incidence of sensitivity to penicillin is something like 25 instances in 10 million patients injected with penicillin. It means that those 25 persons may have been exposed prior to that time by drinking penicillin contaminated milk, or they may have been exposed to previous treatments with penicillin themselves. But regardless, this seems to be the ratio of 25 per 10 million people who are exquisitely sensitive, so this is a hazard as far as exposing humans to the antibiotics that might be present as a residue.

As I reviewed the literature, since I was invited to come before your committee, I found a number of references in which they pointed out that the principal exposure of humans to residue problems is in milk, not in other tissues. I can speak to the other side of the coin, too, and I would like to speak to this because I think your committee can help give guidance to public policy.

Coming from Florida, and in Georgia, Georgia has the recognition of many things, a President, peanuts, but they have a high residue of sulfonamides in the swine carcasses slaughtered there in the State. It has been pointed out, as the Food and Drug Administration has looked at this problem, that it may result from several things: One, the very widespread use of various sulfonamides in swine feeds; two, that the swine producer doesn't clean the feed troughs properly or the feed mills, as they prepare the finished feed, supposedly free of sulfonamides, they don't clean the feed mixes properly, so there is a carryover into the final products of sulfonamides.

Four, they also suggest—and it depends on the size of the farm producer—they suggest that the producer may not properly remove the feces carrying the sulfonamides, and so the animals are guilty of coprophagy, eating their own feces, and they are contaminating themselves; and this is the reason the carcasses are contaminated.

So I would like to suggest that this is a continuing hazard and one that I think, with proper guidance from FDA and the people in the public health departments, that this can be remedied just as the mastitis product problem was remedied.

Other antibiotics, as I looked at the literature, certainly have been shown, as pointed out today, to produce the resistant organisms or that population to expand while the sensitive organisms are decreased as far as the bacterial population during the period of antibiotic exposure.

I reviewed one article, and this data has not been presented today, that I thought it might be of interest to the committee. This is an article that was reported from the University of Illinois by Drs. Segal, Huber, and Drysdale, in which they took four groups of people: One, working closely with swine; two, those that are being exposed to Salmonella infections from other sources; three, a group of people that were not exposed to either; and four, the husband and wife combinations, examined the two populations with the husband bringing the problem home to the wife as far as salmonellosis, and let me speak to these four areas.

They pointed out that it is true that the resistant salmonellosis can be transmitted from animals to man and from man to man—man to woman in this case—so it is possible these organisms under the influence of antibiotics do become more resistant, and this population can translocate from one animal species to another. So I think the several papers that have been presented to date point out the necessity, the importance, to us from a scientific-minded viewpoint, that we do try to reduce this hazard, this potential hazard.

I would say, finally, as I have listened to the presentation, that it seems to me that the law as now written authorizes adequate directives to the Food and Drug Administration to control this problem, if they are given further encouragement from your committee and other committees to look at this problem more thoroughly and explain the importance to the public, to the farm producer, so that this hazard can be reduced.

The material that I presented, was speaking to the adverse effect of drugs. There have been physicians on the witness stand today, and we had a physician there with us at the University of Florida who examined the incidence of drug-related, antibiotics-related, entries of patients into our teaching hospital. This physician had surveyed several hundred patients, and he found that antibiotic-sensitive susceptibility was contributing from 3 to 8 percent of the patients that came into that hospital had been exposed to antibiotic drugs, and they were there because of exposure to drugs, under the treatment of a physician.

There are a number of papers in the literature, as I looked at this area, that show that the number of patients in human hospitals in the United States get an average of 11 to 14 drugs while they are in the hospital. Those in Britain get an average of 8 to 11 drugs while they are in the hospital, and with these pressures, I think this also is another area that should be looked at as far as a public health hazard.

I think this would summarize the material that I would like to present.

[Testimony resumes on p. 390.]

[The paper Dr. Edds referred to follows:]

Adverse Reactions to Drugs; A Review

G. T. Edds, DVM, PhD*

Drugs are those agents used to effectively prevent, cure or mitigate a disease process. As therapeutic agents, they would be expected to produce beneficial results without toxic or adverse effects. However, numerous factors may alter or interfere with the expected pharmacological action of the chemical or drug. Melman, 1971, describes some factors predisposing to drug reactions, or unwanted consequences of drugs such as administration of the wrong drug to the wrong patient in the wrong dosage, form, amount, route, frequency, at the wrong time for the wrong disease. Some 70 to 80 percent of the reactions are predictable, the other 20 to 30 percent are unanticipated. Modell, 1967, presents a very interesting review of drugs producing toxicity in man and animals including strychnine, alcohol, nicotine, opium and morphine, cocaine, marihuana, LSD, caffeine, ergot, mercury, demerol, barbiturates, chloramphenicol, elixir of sulfanilamide, lithium chloride, thalidomide and MER/29.

Lamy, 1971, reported that oxalates, present in many fruits and vegetables, may impair calcium absorption in humans. Similarly, several plants, as oxalate accumulators predispose to decrease calcium absorption, oxalate precipitation in the kidneys, and symptoms of hypocalcemia resembling milk fever in dairy cattle or eclampsia in bitches. The plant oxalates from halogeton, greasewood, pigweed, beets, rhubarb and sorrel produce toxicity directly or may interfere indirectly with calcium absorption.

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Other instances wherein foods may interfere with drug absorption or activity would include milk or its products and tetracylcines; leafy green vegetables and anticoagulants, foods with pressor amines, cheeses and antihypertensive agents; milk and dairy products with cardiac glycosides; brussel sprouts, cabbage, cauliflower, kale or turnips with thyroid extract.

Pressor amines, such as histamine, tryamine, norepinephrine and serotonin have been isolated from certain foods. Bananas, passion fruit, pineapples, tomatoes, and lemons contain such agents. Cheese is the most common food incriminated in these interactions with drugs.

Lancaster, Davies, divided adverse drug reactions into 2 categories: (1) those related to dosage and to a large degree anticipated, and (2) those largely unpredictable caused by infinitesimal dosages. Other side effects include (1) addiction, (2) hypersensitivity, (3) secondary effects, and (4) therapeutic incompatibility. Beam, 1968, classified toxicity due to adverse effects of overdosage-cumulation, intolerance, or idiosyncrasy such as the prolonged apnea caused by succinylcholine in patients with genetically abnormal pseudochloinesterase enzyme. Edds,1974, pointed out that hexachlorophene, in 3-6% concentrations, although widely used as a disinfectant, was highly toxic to young pups with twitchings, increasingly severe convulsions, opisthotonus and death.

"Safer" drugs have a predictable toxic range and the probable degree of severity of toxic reaction can be predicted according to the size of dose given. Factors affecting safety include age of the patient, weight, sex, composition of diet and general health. Some drugs give signals of increasing toxicity, whereas others, such as coumarin anticoagulants do not.

Allergic reactions are due to antigen-antibody reactions. Not all patients become sensitized to allergens while others become highly sensitized. Several substances, in addition to histamine release, may play roles, including serotonin, acetylcholine, and bradykinin. There may be anaphylactic shock to serum sickness syndrome, urticaria, dermatitis, depression of blood forming organs and hepatic reactions. Unexplained fever may be the first sign of hypersensitivity reactions. If treatment is stopped at this period, a fatal result may possibly be avoided.

In one sensitized to penicillin, penicillinase may be used to eliminate the allergen. Corticosteroids have been efficacious, their anti-inflammatory action probably accounts for most of the benefits. It is recognized that they do suppress antibody formation, so in persons or animals with chronic suppurative lesions, they should be used with caution.

Addicting drugs would include morphine, alcohol, amphetamines, cocaine, tranquilizers, barbiturates and in humans, even tobacco. Drug addiction indicates a state of periodic or chronic intoxication detrimental to the individual and to society resulting from the repeated consumption of the drug.

Secondary adverse reactions would include development of moniliasis and/or vitamin deficiency with repeated, continuous dosage with certain antibiotics. Therapeutic incompatibility would occur in patients receiving coumarin anticoagulants and aspirin which greatly potentiates the effect. Similarly, animals on phenylbutazone would have prolonged prothrombin times. It has long been recognized that the antibiotics neomycin, and especially dihydrostreptomycin may cause auditory nerve damage with loss of hearing.

Melman suggests that 30 percent of all hospitalized patients have drug reactions which may double their hospital stay, and 3 to 5 percent of all human admissions are primarily for a drug reaction. Levy, 1973, suggested that 6.7% of all patient admissions in North America result from adverse drug reactions. Potassium chloride, with hyperkalemia, is dangerous to patients with impaired renal function. Gastrointestinal and cutaneous manifestations accounted for 38% of all adverse reactions. About 30% of patients hospitalized in medical departments can be expected to experience one or more adverse reactions during their stay. In phototoxic reactions, the drug potentiates the effects of the wave-length of light which it absorbs. The reaction resembles an exaggerated sunburn, e.g., phenothiazine in cattle. The inappropriate drug may, because of toxicity, cause a disorder to which the patient would otherwise not be subject: ulceration of the intestine from potassium chloride; intramural intestinal hemorrhage from anticoagulants or aflatoxin, retinal disorders from phenothiazine or tranquilizers, cardiac failure from propranolol; liver damage from many drugs; renal tubular acidosis from antibiotics; and aseptic necrosis of bone from corticosteroids.

The long-term effects of certain drugs may not be seen until even the next generation. An example would be the predisposition to uterine cancer in daughters of mothers who had taken diethylstilbestrol some 16-20 years earlier. Phenothiazine or antimalarial agents may concentrate in the lens and cause damage months later. Where ventricular premature beats develop in a patient and xylocaine or lidocaine is given, one may associate the intensification of the arrhythmias with the local anesthetic.

Certain chemical groupings predictably produce drug toxicity. A variety of amino-containing and nitro-containing compounds may produce methemoglobinemia. These are agents like nitroaniline, sulfonamides, phenacetin or acetanilid. Nitrates in water or heavily fertilized crops may also predispose to methemoglobinemia. On the other hand, it is recognized that PABA may interfere with the antibacterial properties of sulfanilamide. Chlorpromazine serves as a multipotent competitive agent to histamine, catecholamine and acetylcholine and is capable of interfering with some of the action of each.

Adverse drug reactions are most frequent in the very young or old patients. In patients 60 to 70 years of age, the risk of drug reaction is almost double that of a person 20-40 years of age. In the newborn, drug-conjugating enzymes in the liver may be deficient, and the rate of absorption from the gut may be different. In diseases of the liver and in acquired renal failure, metabolism and excretion of drugs may be altered.

More than 200 drugs, insecticides, and carcinogens and other chemicals are known to stimulate the activity of drug metabolizing enzymes. Some examples are phenobarbital and griseofulvin, coumarin, anticonvulsants-hydantoin, digitoxin while prior meprobamate dosage enhances its own metabolism on subsequent dosage. Phenylbutazone, pentobarbital and phenobarbital stimulate their own metabolism during chronic administration. Silvestri, 1971, demonstrated that phenobarbital pretreatment of sheep afforded protection against toxic doses of coumaphos. On the other hand, the fat soluble vitamin K, menadione, potentiates the pharmacologic effect of corticosteroids by inhibiting the metabolism of cortisol by liver microsomes.

Not all drug interactions are undesirable. Atropine is known to reduce the toxicity of neguvon in horses, or in dogs. The interaction of BAL with heavy metals has been clinically valuable in animals and man. Protamine sulfate is effective in reversing the action of heparin.

The antibiotics are the most frequently prescribed drugs, about 50 percent, in the U.S. It was estimated that one out of every four people in the U.S. received penicillin each year and that 90% of the drug was wasted. Fortunately, not more than 25 of every 10 million penicillin injections lead to serious consequences. Three of these 25 however may be fatal. Further, the only adverse reaction to penicillin in foods has been its presence in milk (Hewith). However, they have introduced new disease problems, such as tetracycline staining of teeth, Cohlan, 1977, and penicillin sensitivity. As little as 1 gram per day of tetracycline for 3 days during the third trimester can produce yellow staining of deciduous teeth, as elicited by use of a Wood's lamp. Oxytetracycline is said to produce less staining than chlortetracycline and tetracycline. The tetracyclines can cause sudden death with hepatic necrosis if given intravenously to patients with renal impairments.

Kagan, 1973, reviewed the very important penicillin antibiotics methacillin, oxacillin, nafcillin, dicloxacillin, and ampicillins which are penicillinase resistant, are available in parenteral and oral forms; ampicillin is effective against both gram-positive and negative bacteria. A fever that appears first within 48 hours after surgery suggests bronchopulmonary infections; if it starts 3 to 5 days after surgery, it suggests a urinary tract infection. Fever from wound surgery usually appears 4-9 days post-operatively.

The fungistatic antibiotic "amphotericin B", the most effective agent against systemic candidiasis, aspergillosis, histoplasmosis and cryptococossis, may produce toxicity including nausea, vomiting, anxiety, and abdominal pain. "Griseofulvin", used for treating skin fungi, including microsporum, trichophyton and epidermophyton, may also cause dry, painful or black tongue, anorexia, epigastric pain, nausea, vomiting and bloody diarrhea. "Erythromycin", a bacteriostatic agent, may also cause stomatitis, nausea, abdominal pain, diarrhea and alcoholic intolerance. Penicillin G may produce fever, hypersensitivity reactions and immediate anaphylaxis. Proteinuria may be produced.

In case of anaphylaxis in humans sensitive to penicillins, Pankey, 1967, recommended aqueous epinephrine 0.1%, 0.5-1.0 ml methyl prednisolone 40-125 mg and diphenhydramine, 50 mg, intravenously through the tubing of a 5% dextrose infusion. Penicillinase was not used.

Chloramphenicol is the leading cause of drug-induced aplastic anemia. It may also produce acute and fatal collapse in patients deficient in hepatic conjugating enzymes as well as cause serious visual disturbances. Polymyxin B, used for systemic infections caused by pseudomonas or other gram-negative bacilli, may produce circumoral paresthesia, nystagmus, ataxia and dysarthria. Nitrofurantoin used for urinary infections, may cause nausea, vomiting, drug fever, rashes, anaphylaxis and anemia. Streptomycin may induce hypersensitivity with dermatitis, fever, eosinophilia, vestibular dysfunction, vertigo and ataxia. Streptomycin should not be used in anesthetized patients.

The sulfonamides, including sulfadiazine and sulfisoxazole, may induce nausea, vomiting, dizziness, agranulocytosis, hepatitis, anemia, cyanosis from met- or sulf-hemoglobinemia, photosensitivity, kernicterus in new-born infants, fever, dermatitis and anaphylaxis. The tetracyclines may cause nausea, vomiting, anorexia, diarrhea, flatulence, and stomatitis, vaginitis and proctitis as a result of candidiasis. Because the intestinal flora is altered, there may be a decrease in synthesis of Vitamin K and a deficiency of riboflavin. A multivitamin preparation should be given daily along with the tetracyclines.

Irey, AFIP, 1974, reported on the comparative incidence of deaths from single drug overdosage and indicated these agents are most frequently found: barbiturates 27, morphine 28, propoxyphene 27, salicylates 18, methadone 17, chloroquine 15, and glutethimide 14, of a total of 146 cases. Thus, it is now as important to recognize the presence of adverse drug reactions as it is to recognize malignancy, infection, metabolic abnormality or other disease processes. Drugs and chemicals may: (1) produce degeneration and necrosis of cells, (2) stimulate tissue to hyperplasia and neoplasia, (3) be associated with acute, subacute, chronic or granulomatous inflammation, or (4) be associated with mutagenesis or teratogenesis.

Scott, 1974, pointed out that the average hospitalized patient in the U.S. receives 11 drugs during his stay, while those in Britain receive 6. In Britain, 13.6 percent of 2066 patients monitored suffered adverse drug reactions and of these 15 percent were due to serious drug interactions. Certain drugs should art be combined because of physical incompatibility, e.g., lidocaine and alkaline solutions, aminophylline and barbiturates, ampicillin and saline solutions, aminophylline and barbiturates, ampicillin and saline solutions, chlorpromazine and barbiturates, vitamin B complex and antibiotics, and aminophylline or warfarin.

There may be interference with absorption due to change in pH, sodium bicarbonate and tetracyclines or mineral oil and vitamins A & D; propantheline slows absorption of sulfonamides because of decreased motility. Chelation of Ca^{++}, Fe^{++}, Mg^{++}, Al^{++} ions reduce tetracycline absorption and vice versa. Kaolin reduces absorption of most drugs. Neomycin induces a malabsorption syndrome with delayed absorption of ampicillin.

Plasma protein binding displacement enables phenylbutazone to potentiate the action of warfarin on coagulation in dogs (Bachman, 1975). Because of competition and potentiation at receptor sites, Vitamin K antagonizes coumarin anticoagulants. Ethanol, antihistamines and tranquilizers potentiate the central nervous depressant action of one another. By interfering with excretion, probenecid inhibits the excretion of penicillins, dapsone and indomethacin. Sodium bicarbonate decreases the excretion of amphetamine.

Teary, 1966, compared the toxicity of several commonly used drugs in newborn and adult rats. In general, the CNS of the newborn animal is less sensitive to the toxic effect of stimulant drugs than the mature rat. However, CNS depressant drugs were more toxic in the newborn rat. Although lead arsenate and arsanilic acid were more toxic in the newborn, lead and arsenic were found to have an additive toxicity. The newborn animal was more sensitive than the adult to acute toxicity of anticholinergic drugs. Dicoumarin was more toxic to the newborn than the adult; in this instance there was correlation between the immature rat and infants.

Girdwood, 1971, reviews beneficial and detrimental results from drug interactions. Isoniazid plus p-aminosalicylic acid are given with streptomycin in tuberculosis so that resistant strains will not emerge. Sulfamethoxazole with trimethoprim prevents DNA synthesis by bacteria; the sulfonamide inhibits the enzyme involved in the incorporation of PABA into the dihydrofolic acid molecule and trimethoprim inhibits dihydrofolic acid reductase. Also, probenecid may be used to slow down the excretion of penicillin. On the other hand, the phosphates and calcium interfere with absorption of iron from the gut. If barbiturates are given together with warfarin or coumarins, the enzymes that destroy the anticoagulants are stimulated, and the dosages have to be increased. If administration of the barbiturate is then stopped and the dosage of the anticoagulant not reduced, severe bleeding may occur. The dangers of combining monoamine oxidase inhibitors with sympathomimetic drugs or the consumption of cheeses or wine consumption are well known.

Roe, 1971, elaborates on the incidence of drug-induced vitamin deficiencies and suggests methods of reducing these hazards. Women taking oral contraceptives had a lower level of serum folate than control persons; most women absorb enough folic acid to prevent megaloblastic anemia. The anemia patients showed favorable response to orally administered 250 µg folic acid per day. Continued use of antiepileptic drugs in humans may also induce a relatively high incidence of megaloblastic anemia. Prophylactic treatment of all epileptic patients with folic acid and Vitamin B_{12} is recommended.

Folic acid is an essential precursor of a number of cellular enzymes, including the pathway for synthesis of DNA. Deoxyuridylic acid is methylated to form thymidylic acid which is an essential pyrimidine nucleotide of DNA. The CH_3 group needed for this reaction is donated by the enzyme N^5, N^{10} - methylene tetrahydrofolic acid. During methylation, the coenzyme is converted to dihydrofolic acid which must be reduced to tetrahydrofolic acid before the coenzyme can be reformed to complete the cycle. Thus, methotrexate depresses cell turnover, including tumor cells, but it also inhibits other cells of the epidermis, bone marrow, and intestinal mucosa.

Isonicotinic acid hydrazide, an antituberculosis agent, may produce neuritis in patients receiving the drug, by reducing the pyridoxine levels through increased kidney losses. Daily administration of 50 mg pyridoxine prevents neuritis. Higher levels of the hydrazides may lead to convulsions and death - pryidoxine is the antidote.

The chelating agent, penicillamine, also forms complexes with pyridoxine and convulsions, associated with vitamin B_6 deficiency, may ensue. Riboflavin deficiency predisposes to the adverse effects of boric acid absorption while a high intake of riboflavin gives protection against boric acid toxicity in experimental animals. Boric acid acts as a teratogenic substance with skeletal malformations in chick embryos when boric acid is injected into the yolk-sac.

In summary, Smith, 1972, suggests that adverse drug reactions are not confined to the hospital community, but that reactions to drugs inside and outside the hospital should be investigated further. Whether treating humans or animals, it is important that one observe both the hazards as well as the potential benefits of drug therapy. The earlier an adverse reaction is recognized, the sooner suitable action can be taken to minimize or alleviate the undesirable side effects.

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Food	**Agent**	**Signs**	**Treatment**
Almonds	Amygdalin (HCN)	Tissue Anoxia	Sod. nitrite/thiosulfate
Apricot jam	Kernels (HCN)	Emesis, convulsions	Same
Bagasse		Pneumoconiosis, fever & cough	Antihistamines
Buttermilk		Impalatable	
Buckwheat		Fagopyrismus, enteritis vomiting, diarrhea, convulsions	
Cashew nuts		Dermatitis, blisters of lips and tongue	
Cassava	Aflatoxin	Carcinogen- hepatitis, stunting	
Coffee	Caffeine	Gastroenteritis, diuresis, premature systoles	
Cigars	Nicotine	Periferal vasoconstruction, tremors, resp. stimulation, depression, death due to respiratory failure	
Dextrose	Hyper onic	Hemolysis on i.v. injection	
Fava bean	Vicia fava beans, pollen	Acute febrile anemia jaundice, hematuria	
Fat	Embolism	Rigor, cough, confusion	
Fish	Mullet, pompano herring, grouper barracuda, puffer	Tingling, fingers, hands, feet Ataxia, chills, fever	Cook fish well
Fish, stings	Catfish	Redness, local inflammation swelling, hemorrhages, paralysis, death	
Fish, shell	(Crabmeat, Mussel)	Respiratory paralysis, severe diarrhea	
Ergot	Alkaloids	Gangrene, convulsions	
Honey Poison	Oleander, laurel		
Jerusalem Cherry	Solanine		
Milk		Hypercalcification, insomnia hyperirritability, loss of weight, anemia	
Hemlock, water	Cicutoxin	Nausea, vomiting, convulsions	
Mushrooms	Phalloidine	Convulsions, gastralgia, nausea retching, vomiting, diarrhea	Atropine, saline Cathartics

Foods	Agent	Signs	Treatment
Juices/soups	Antimony lead, arsenic Cadmium, mercury	Vomiting, Abdominal Pain diarrhea, thirst, convulsions	BAL, Cathartics
Nutmeg	Myristicin	Narcotic, stimulation, euphoria, toxic psychosis	
Peas, Sweet		Leg weakness, nerve cell degeneration	
Pea, Rosary	Jequirity bean	Gastroenteritis, vomiting	Saline, Cathartics
Peyote	Mescaline	Visual hallucinations, no erotic impulses	
Plastic cheese	Plastic	Fatal hemorrhage-sharp edges	
Potato	Solanine 9-20 mg/100 gm.	Vomiting, diarrhea, malaise	"Tr. of time"
Rhubarb	Oxalates	Cramp-like pains, slow clotting, nausea, vomiting	Gastric lavage Milk-limewater
Royal Jelly	Honeybees	No action; stimulates I.Q.?	
Snakeroot	Trematol	Weakness, prostration, vomiting, severe constipation	
Tea	Tannic Acid	Gastroenteritis, constipation	
Yam, wild	Dioscoreine	Burning in throat, vomiting, drowsiness	
Yaupon	Alcohol	Emetic and cathartic	
Tomato Juice	2 years	Orange-yellow skin color, nausea, vomiting, diarrhea	Discontinue

Foods	Agent	Signs	Treatment
Tea	Tannic acid	Gastroenteritis, constipation	
Tomato Juice	2 years	Orange-yellow skin color, nausea,vomiting, diarrhea	Discontinue
Vitamin A	1,000,000 I.U.	Anorexia, pruritus, headache In children-cannot give 200,000 units/day	
	150,000 I.U.	Daily-adults + loss of hair and scalp,eyebrows, axilla	
Vitamin D	Infants>1,800 units daily Children>40,000 " " Adults>100,000 " "	Toxic-anorexia, fatigue Nausea, headache, polyuria, diarrhea, anemia, loss of weight	
Toxicity of Traditional Christmas Greens			
Bittersweet, European		Very toxic	
Jerusalem, cherry		Very toxic	
Jequirty bean		Highly toxic	
Mistletoe, American		Moderately toxic	
Yew		Moderately toxic	

Mr. **Waxman**. Thank you very much.

Dr. Visek?

STATEMENT OF WILLARD J. VISEK, M.D., PH. D.

Dr. **Visek**. Thank you. I didn't know I was going to be next.

First of all, for the record, I am listed as a veterinarian, which is incorrect. I am a licensed physician who spent 11 years in the department of animal science at Cornell. I have a Ph. D. in animal nutrition, and presently am head of nutrition and metabolism at the University of Illinois School of Clinical Medicine and professor of food science, Urbana-Champaign.

I have been a member of the regulatory agency committee of the American Society of Animal Science since 1972, and have been their subcommittee chairman on antimicrobials for 6 years. In June 1979, the society sent me as their representative to the United Kingdom, to Germany, and to Holland, to study the antibiotic resistance problem as it relates to antibiotic use in animal feeds.

Historically, you may recall that in 1971 Britain adopted the Swann regulations to limit the use of antibiotics in animal feeds much as you propose in H.R. 7285. The purpose for my trip was to find out what the experience may be in those countries, based on their practices where antibiotic feed use has been limited to either European Economic Community regulations or the Swann regulations in Britain.

Before going further, I might point out that paragraphs 3 and 4 of the proposed bill under section 2 are not justified by scientific evidence, and I think paragraph 6 likewise makes assumptions for which we have no evidence.

The laboratories I visited in 1979 in Britain were the Central Veterinary Laboratories, who administer the Swann regulations and decide what antibiotics shall be used in animal production in Great Britain.

Then I visited the Poultry Research Station in Huntington, and the Central Public Health Laboratories in London, and then proceeded to the Medical School at the University of Bristol. From there I went to the National Institute of Public Health in Holland, and the Institute for Veterinary Medicine in Berlin, in West Germany.

We were particularly interested in finding whether there has been any beneficial impact of the regulations adopted following the Swann report in Britain.

As you may recall, there was an episode of infected calves in 1965 with strain 29 organisms, which were the result of therapeutic use and not feed use. In fact, in 1979, in June, they had a farm localized in England where a similar incident had taken place, but now they had strain 43, which was a combination of strains 204 and 193. Thus they had developed a strain of resistant organisms again in England as in 1965, and it was again an outcome of therapeutic use.

I think the revealing information was supplied by Dr. Rowe, who directs the Public Health Laboratories in London that receive something like 20,000 cultures from veterinarians, hospitals, infections in man, and infections in animals. This is the annual number of specimens they receive for testing. They do serotyping as well as resistance on all of these cultures, and Dr. Rowe's conclusion was that they had no evidence that any of the resistance problems were related to feed use of antibiotics. He didn't say they weren't, but they haven't been able to find evidence that they were.

This is the Enteric Pathogen Laboratory of England. It is also a referral center for WHO for various cultures of organisms.

There is no question that *Salmonella typhimurium* is a major problem, and it is acquired from livestock, principally from cattle, and that is the source of the human infection. There is no question about it for England.

Salmonella typhimurium has a high percentage of resistance or resistant strains, and that is more true of that particular organism than other species of Salmonella, and no one knows why. Again the concluding statement from Dr. Rowe was that feed use could not be established as the reason for the problem and that there were other practices in animal production that were responsible. Therapeutic use of antibiotics was a major problem, and that it was a problem not only in Britain, but was being exported to the continent, where there were other problems arising with Salmonella in human populations due to therapeutic use.

I think one of the revealing bits of evidence I was able to obtain was in Professor Richmond's laboratory at Bristol, where he actually tested organisms in the sewers of Bristol and England and found resistant E. coli. He went to the health services and was able to establish that much of this arose principally from therapeutic use by physicians that were outside of hospitals in Bristol, prescribing tetracycline for nonspecific urethritis and other diseases.

So I think the conclusion certainly was, by everyone I talked to, that the Swann regulations do not work in England.

And then in Holland there is a different story. In Holland, because of European Economic Community regulations, they started to restrict the use of tetracycline in feeds in Holland in 1974, and if you look at the data, there is evidence that there may have been a decline in resistant organisms collected there and in Germany.

The circumstances of animal production are considerably different in those countries. Holland is a very low country with a high water table. This creates problems with sanitation in animal production. They found that among the really serious problems in the spread of organisms was the way meat and other products were handled in the household and in the kitchen.

I think Professor Bulling in Berlin was quite emphatic. He felt that restricting the use of tetracyclines in feed did have influence on reducing the number of resistant organisms in the environment, but, again, this is for a different country and I am not sure how their experience would fit our conditions.

I am sure however, that H.R. 7285, as proposed, would assure us that the public health of this country would be protected. I don't think we have the evidence to know the problem well enough to know what kind of legislation to adopt at the moment, I don't see that this bill would help us.

We talk about substitutes for antibiotics in animal production. If we take out of feed penicillin and tetracycline, we have no substitute to deal with diseases like anaplasmosis, shipping fever, and liver abscesses in cattle, and atrophic rhinitis in swine.

Legislation can be adopted to require a veterinarian prescription for control of some of these problems to circumvent feed use. But remember the microorganisms don't know the difference. They are going to get resistant whether antibiotics are prescribed by a veterinarian or not. The important factor is they are going to have to be used until we find some other means of controlling the problems facing animal producers.

We have to use these agents to control these diseases, and we have a lot of problems we don't understand. We are not prepared to adopt legislation at this time.

[Testimony resumes on p. 403.]

[Dr. Visek's prepared statement follows:]

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(217) XXXXXXX 333-0119

June 6, 1980

The Honorable Henry A. Waxman, Chairman
Subcommittee on Health and Environment
512 Annex 1
House Office Building
Washington, DC 20515

RE: H.R. 7285 Introduced to Amend the Federal Food, Drug and Cosmetic Act to Limit the Antibiotic Drugs Which May Be Used in Subtherapeutic Doses in Animal Feed

WRITTEN FOR THE RECORD

Dear Congressman Waxman:

I have asked for permission to present, in person, knowledge about the issues which this bill proposes to address. According to information from Congressman Dingell's office, there will be no time on June 12 and 13 to receive my oral testimony at the hearings.

I have done research on the mode of growth promotion by antibiotics in animals since 1958 and have served as a member and Chairman of the Subcommittee on Antimicrobials of the Regulatory Agency Committee, American Society of Animal Science since 1972. My Curriculum Vitae is attached.

Most of the information summarized herewith was obtained in my travels to Britain and Europe in 1979 as a member of the Subcommittee representing the Society to obtain information about the health aspects of antibiotic use in animal production. My expenses were covered by the American Society of Animal Science.

Before summarizing the information from the UK and Europe, I wish to point out that the statements made in Parts (3) and (4) of Section 2 of the proposed bill are not supported by scientific evidence and that part 6 makes assumptions which do not agree with the experience in Britain and Europe nor can they be assumed for the United States.

During June 10-20, 1979 I visited the following laboratories: (1) England: Central Veterinary Laboratories (CVL), Weybridge; Houghton Poultry Research Station, Huntingdon; Central Public Health Laboratories, London; and the

Department of Bacteriology, The Medical School, Bristol. (2) Holland: National Institute of Public Health, Bilthoven. (3) West Germany: Institute for Veterinary Medicine. More complete information about the laboratories and the individuals visited is attached. Highlights of the discussions are included here. Published data are in the cited references.

Much of the information obtained in Britain related to experience since 1971 when the Regulations following the Swann Report were adopted to categorize antibiotics as therapeutic for use in treatment of disease and those permitted as growth promotants if they had no demonstrated ability to induce multiple drug resistance or resistance to chloramphenicol, the drug of choice for treating S type or S paratyphi infections. Veterinarians in Britain may prescribe any antibiotic they deem appropriate but therapeutic antibiotics are illegal for growth promotion or prophyllaxis. It is significant that of the 6000 Veterinarians practicing in Britain 4000 are in large animal practice. In the U.S. as of June 30, 1978, veterinarian members in the American Veterinary Medical Association (AVMA) totaled about 31,000, about 13,000 reported some large animal practice. Only about 2100 limited their practice to large animals. About 80% of all veterinarians in the U.S. are AVMA members.

My discussions were principally with scientists including veterinarians or physicians who have data and are not relaying anecdotal observations or clinical impressions. With one exception they gave evidence that E. coli or Salmonella isolated from animals in Britain show no decrease in tetracycline (Tc) resistance since the Swann Regulations were adopted. Dr. H. Williams Smith, the exception, stated that he sampled 100 stools of animals at a sales barn in his area each autumn. In 1970 65% showed all E. coli to be resistant and in 1978 34%. However, all specimens always showed some Tc resistant E. coli. The CVL in Weybridge has examined about 27,000 Salmonella strains since 1971 with 15,000 coming from cattle. The percentage showing resistance to 8 antibiotics has not declined.

The Enteric Pathogen Laboratory of the Central Public Health Laboratory directed by Dr. Bernard Rowe does complete cross typing and serotyping of Shigella, Salmonella and E. coli strains isolated in the British Isles. Strains come from 60 public health laboratories, hundreds of other laboratories, and the Veterinary Investigation Service. The total strains per year include 20,000 Salmonella of which 50% will be S. Typhimurium, 5000 Shigella and 6-7000 E. coli. Salmonella are the main problem.

In 1977 strains of S. typhimurium, S. hadar, and S. enteridities accounted for 50% of all human infections. Ninety-two percent of the S. typhimurium strains came from cattle and 42% of S. hadar strains came from turkeys. Pigs rank next to cattle as a source of S. typhimurium infections in man. According to Dr. Rowe, Salmonellosis in man can always be traced to animal sources. Antibiotic resistance in S. typhimurium is as follows: human strains 20%, bovine 60%, pigs 20-30% and food producing animals 10%. In 1977 60% of bovine strains were resistant to one antibiotic, 32% to two; 4% to three and 17% to four. In 1978 directorship of the laboratory changed and now all serotypes are studied for drug resistance contrary to earlier years. In 1978 80% of all S. typhimurium strains from cattle showed resistance to some antibiotics compared to 30% in 1977 despite the fact that Swann regulations remain in force. Dr. Rowe pointed out that S. typhimurium phage type, 29 which arose from calves to cause the outbreak in 1965, has disappeared but phage types 204 and 193 common now in man and endemic in cattle arose from a single clone carrying a plasmid for tetracycline resistance. Rowe pointed out that the farm where this occurred with therapeutic use of antibiotics is known. Rowe cited a similar result of therapeutic misuse of antibiotics in France which have led to severe infections in pediatric hospitals by S. wien which has greater resistance and greater pathogenicity. In agreement with Professor Linton at Bristol and the CVL, Dr. Rowe pointed out that stress and transportation of animals increase the incidence of infections and shedding of Salmonella.

The Department of Bacteriology under Professor Richmond at Bristol has done extensive work on Tc resistance in E. coli. Professor Richmond's letter to the Hearing Clerk, here attached, expands on his findings that medical use of Tc in man creates a major reservoir of antibiotic resistant E. coli in the environment and that restricting feed use would not reduce the magnitude of the problem. Professor Linton expressed the view that the post Swann Regulations do not work because veterinary use of antibiotics continues to impose selection pressure which maintains an antibiotic resistant reservoir in the environment.

Data in Holland revealed that the number of tetracycline resistant strains of Salmonella from swine and man has declined since 1974 when Tc use in feeds was banned. However, resistant strains from calves have not decreased because of therapeutic use. Of interest, 25% of the pigs in Holland carry S. typhimurium without evidence of disease.

Data reviewed in West Berlin with Professor Bulling have been derived since 1965. Dr. Bulling fed swine 20 ppm of chloramphenicol for 8 weeks and gave them 10^8 S. typhimurium organisms that were chloramphenicol sensitive. The pigs that became sick with Salmonellosis as evidenced by fever excreted Salmonella with chloramphenicol resistance plasmids which were acquired from E. coli. Bulling has data showing a decline in Tc resistance of S. typhimurium since Tc was banned from animal feeds by the EEC in 1974.

The following conclusions are supported by the information derived from my meetings in Britain and Europe.

1. Swann Regulations do not work in Britain.
2. Salmonella typhimurium is the primary problem in cattle and acquires its resistance plasmids from other organisms mainly from E. coli.

3. Stress, therapeutic use of antibiotics, transport and concentration of animals cause shedding and spread of Salmonella infections.

4. A substantial percentage of animals can carry resistant Salmonella without clinically evident disease.

5. Therapeutic use of tetracyclines in man is a major contributor to the antibiotic resistance problem.

6. Salmonella contamination can arise from cold and warm-blooded pets, animal protein used for feed, slaughtering operations, and poor handling of meat in the kitchen. It generally causes gastroenteritis which need not be treated unless there is fever. Resistant organisms complicate therapy when that happens.

7. Feed use of antibiotics is only one contributor to a major antibiotic resistance problem.

8. The severity of the antibiotic resistance problem varies by country due to population density, climate, topography and management practices.

9. The evidence in Germany and Holland shows that restriction of feed use of tetracyclines corresponds with a decrease in the number of strains isolated from swine that are resistant. Similar trends appear in men in Holland.

10. Solution of the antibiotic resistance problem will require data on the contributions of use and misuse in feeds, veterinary practice and medical practice.

11. Resistance is determined by overall selection pressure, mainly by the dosages of antibiotics used at a particular site in the environment and less so by the total quantity used in a particular geographic area.

12. E. coli is a commensal organism in man and animals in a relationship that can be disturbed only within certain limits. Presence of Salmonella is not normal and practices should be employed which minimize its presence.

My experience in research and the information I obtained on my special trip to the UK and Europe convinces me that HR 7285 as proposed will not protect the health of the public and is undesirable.

Sincerely yours,

Willard J Visek

Willard J. Visek, Ph.D., M.D.
Professor of Clinical Sciences
(Nutrition and Metabolism)
Professor of Food Science

WJV:bhw

Enclosures

cc: R. J. Gerrits

Supplementary Information on Trip to United Kingdom, Holland and West Germany
June 10-20, 1979

Willard J. Visek, M.D., Ph.D.

I. Laboratories Visited

The following laboratories were visited during the period of June 10-20, 1979.

Date	Laboratory	Individuals Visited
6/11/79	National Institute for Research in Dairying (NIRD) Shinfield, Reading, RG2 9AT England	R. Braude, Head Pig Husbandry Department Phone: 0734-8831303 ext. 287
6/11/79	Central Veterinary Laboratories Weybridge, England	Brindley Morgan, DVM Deputy Director W. J. Sojka, DVM & R. S. Cameron, DVM Research Scientists
	Important individuals at Weybridge not available (Dr. G. Davies and Timothy Stevens, DVM, who is the Director)	
6/12/79	Houghton Poultry Research Station Houghton, Huntingdon, Cambs., PE England 17 2DA	H. Williams Smith, DVM
6/13/79	Enteric Pathogen Laboratory Central Public Health Laboratory Colindale Avenue London NW9 5HT England	Dr. Bernard Rowe, M.D. Director Phone: 1-205-7041
	Also WHO International Collaborating Center for Drug Resistance of Enterobacteria	
6/14/79	Department of Bacteriology The Medical School University Walk Bristol BS8 1TD	Professor M. H. Richmond, Ph.D., Sc.D., Head Professor A. H. Linton, Ph.D. Phone: 0272-24161

6/18/79	Rijks Institut Voorde Volksgezondheid Antonie van Leewenhoeklaan 9 Postbus 1 Bilthoven, The Netherlands (National Institute of Public Health)	Dr. P.A.M. Guinee, DVM Phone: 030-78-91-11
6/19/79	Institute for Veterinary Medicine des Bundesgesundheitsamtes Postfach 1000 Berlin 33, Germany (Also WHO Center for Food Hygiene. Also Republic of Germany Center for Salmonella registration in feed stuffs and egg production started in 1961)	Professor E. Bulling, DVM R. Stephan, DVM Phone: 49-30-83-08-471

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PROFESSOR OF BACTERIOLOGY
M. H. RICHMOND M.A., PH.D.

MHR/SEC 1st.October, 1978

Dear Sir,

I have just had a chance to have a relatively brief look at you Draft Environmental Impact Statement : "Sub-therapeutic Agents in Animal Feeds" and I feel I must let you have a few comments. Before doing this, however, I would like to stress two points : first, these remarks have had to be assembled hurriedly. I saw the Draft Statement for the first time on 29th. September and if the document I am now writing is to have any chance of reaching you before your dealine of October 6th. it will have to be despatched tomorrow. Secondly, I would like to stress that my view of the situation is likely to be coloured by my being much more familiar with the scene in the U.K. than in the U.S. Indeed, it could well seem somewhat presumptious of me to write about what is essentially a matter domestic to the U.S. That I am commenting at all is partly because a substantial amount of work from this Department has been quoted in the Statement; but mainly it is because I feel there are a number of important omissions from the document and these could well have important consequences when the time comes - as it surely must - for making the final risk/benefit analysis.

The crucial omission from your Statement in my view is an analysis of the current situation in man, and in particular of the consequences of the human therapeutic use of antibiotics on the incidence of resistant bacteria in the human population. To try to consider the impact on human health of changes in policy with respect to animal use without discussing the extent to which the reservoir of resistant bacteria in man reflects human use, is like trying to obtain stereoscopic vision with only one eye; it simply cannot be done.

Over the last few months, we in Bristol have been trying to assess the impact of human tetracycline therapy on the incidenceof tetracycline resistance in man. Our approach has been to discover the amount of tetracycline used in human therapy in the Bristol area, and then to establish on a sample basis where it was used, and for what purpose. Work already freely available in the literature shows clearly that the treatment of human beings with a standard course of tetracycline results in the appearance of a predominantly tetracycline resistant E.coli gut flora of the people under treatment after about 36 to 48 hours. Moreover, this situation is likely to persist during the duration of the treatment. But what is of greatest importance in the present context, is that the gut flora of people receiving therapeutic courses of tetracycline usually remains predominantly resistant for several days after treatment has ended; and on occasion this situation may persist for months or even more than a year. I do not have the space here to give an analysis of our data in detail. Suffice it to say that one has made the following important observations in relation to tetracycline and its use in man :

1. It seems highly probable that a substantial proportion of people receiving tetracycline therapy as in-patients in hospitals are discharged before the rich tetracycline resistant flora in their alimentary tracts has been dissipated.

2. If one calculates the number of people outside hospital in Bristol who, at any one time, are carrying this rich tetracycline resistant gut flora as a result of human tetracycline therapy, it amounts to about 0.6% of the population

Published work in which we examined the incidence of tetracycline resistant E.coli in the Bristol sewers, showed that this value is reasonably close to the the incidence of tetracycline resistant coliforms in sewage coming from domestic housing areas. So, in the context of environmental impact, there seems to be no need to implicate a strong flow of resistant E.coli from farm animals as a source of tetracycline resistant E.coli in man. Of course, such a flow does occur, but the evidence is increasingly that its impact is quantitatively small for E.coli when compared with what arises from human therapy. Moreover, the strains selected in man by human therapy are likely to be better adapted - on average - to survive in man, than strains of animal origin. I feel the relevance of this data to your discussion must be obvious: the quantitative aspects of the matter will have to figure largely in any risk/benefit analysis.

In passing, it is perhaps worth stressing that I feel the impact of human therapeutic use of antibiotics is also seriously underestimated by the writers of the issues of the Federal Register where cases "against" penicillin and tetracycline are made. I do not feel, for example, that the typhoid outbreak in Mexico, or the appearance of the penicillinase-producing gonococci in Manila, can possibly be thought of as a consequence of the use of antibiotics for animal feed purposes. In both cases, the use of antibiotics for human therapy, much of it doubtless indiscriminate, provided the selection pressure.

There are numbers of other omissions from the analysis in the Draft that I think important. I feel the authors underestimate the extent to which Gram-negative bacteria - notably E.coli - are already widely resistant in animals being housed under intensive rearing conditions. Some of the data given in Appendix A certainly speak to this point; but the main question that arises as a result of this information is: if one does limit the use of tetracycline and penicillin in animal feed, is one sure the situation will improve? Are we not so far down the road that recovery will at best be slow ? If we take data from the Bristol area and compare the situation now with what obtained before the implementation of the Swann Committee's recommendations in the U.K., we find little difference in the incidence of tetracycline resistant bacteria then and now. There are, of course, several interpretations that can be put on this observation. First, the regulations may not be being obeyed. Or perhaps the truly therapeutic use of tetracycline in farm animals is still adequate to maintain the high incidence of resistant bacteria. Or perhaps the bacteria in question has already evolved under the impact of selection pressure to the point at which a great majority of the members of the E.coli flora have added a broad resistance pattern to those other characteristics which make them good colonisers of animals under intensive rearing conditions. This is not so far fetched. Intensive rearing procedures usually use uniform genetic strains of animals in a highly uniform and reproducible environment. Is it perhaps possible that such a narrow range of selection pressure, including as it does antibiotic administration, may not by now have led to the evolution of "totipotent bacteria" which are able to persist for long periods, whether or not antibiotic selection pressure is applied ? Nor is it totally irrelevant to point out that we may currently be seeing a similar situation developing in man. The one place where man can approximate his lifestyle to an intensive rearing unit is when he is in hospital. And it is there that clones of resistant bacteria - often very difficult to displace by changes in antibiotic use - cause most trouble to man. In summary then: what is proposed in the issues of the Federal Register with respect to penicillin and tetracycline use simply may not work - and for reasons not discussed adequately in your Draft.

Finally, I do not think your Draft distinguishes adequately between the ecology of E.coli and Salmonella species. The former are commensal in the guts of man and higher animals: the latter are not. This distinction seems to me to be important because it leads to a clear difference of objectives - commercial producers aim to have feed animals free of Salmonellae but not of E.coli. Furthermore, the objective of having feed animals free of Salmonella holds whether the organisms are resistant or not; and indeed methods of husbandry have been evolved which do achieve this for long periods. Similarly, public health measures by and large keep the human populations free of salmonellosis. So I think it has to be argued why one talks of altering antibiotic use with respect to Salmonella, when the prime concern surely must be to grow food animals free from all Salmonella. Were this to be achieved consistently, the chance of human salmonellosis would be greatly reduced.

To my mind this line of thought is important because it leads one to realise that the use of antibiotics, and their impact on human and animal pathogens should be the main factor in trying to control the ecology of a class of organisms only when their main relevance is as a commensal.

I should like to end by congratulating the authors of your Draft on the extremely successful way in which they have tackled such a voluminous literature, and moreover, a literature where the issues have been so hotly contested. Even in the areas I have singled out for comment, I suspect that the authors could have said more. However, the first issue I raise, in particular, must be very close to the central problem which will face the Hearing Judge in due course, and one can understant the authors reluctance to deal with matters which may be so germane to the hearings, yet where the hard evidence is so scanty.

Yours faithfully,

M.H.Richmond

The Hearings Clerk,
Food & Drug Administration,
Room 4-65
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U.S.A.

Transfer of Antibiotic Resistance in Salmonella Strains
(Federal Health Office, West Germany)

Years	1961	1970	1971	1972	1973	1974	1975	1976
No. Strains	1000	1487	1855	2273	2892	2192	1892	3043
% resistant	2.5	9.5	12.1	13.3	24.4	26.9	15.4	12.1
S. typhimurium (Volltyp) mainly calves	6.8		32.3	37.5	63.6	52.0	36.0	35.8
S. typhimurium varcopenhagen (mainly pigeons)	2.0		9.6	3.1	6.4	4.7	4.3	4.3
S. panama			65.6	57.3	52.1	22.1	6.7	1.6
S. dublin	0.6		2.6	0.7	6.9	16.0	70.0	69.9

Reprints by Dr. Bulling:

R. Stephan, E. Bulling and A. Steinbeck. Zbl. Bakt. Hyg., I. Abt. Orig. A 237, 264-273, 1977.

R. Stephan, E. Bulling and A. Steinbeck. Zbl. Bakt. Hyg., I. Abt. Orig. A 237, 254-263, 1977.

E. Bulling and R. Stephan. Zbl. Vet. Med. B, 19, 268-284, 1972.

R. Stephan, E. Bulling and A. Steinbeck. Zbl. Bakt. Hyg., I. Abt. Orig. A 234, 29-36, 1976.

R. Stephan, E. Bulling and A. Steinbeck. Zbl. Bakt. Hyg., I. Abt. Orig. A 234, 37-45, 1976.

Mr. WAXMAN. Thank you very much.

Mr. Lambert?

Mr. LAMBERT. Mr. Chairman, if I might defer to Dr. Hewitt initially.

STATEMENT OF WILLIAM L. HEWITT, M.D.

Dr. HEWITT. Mr. Waxman, and members of the committee, I am professor of Medicine and chief of the Division of Infectious Diseases, School of Medicine, at UCLA. My watch says 12:30, and I have had my lunch, so I feel I probably have the rest of the afternoon to talk.

Mr. WAXMAN. Let me warn you, the jet lag may still hit.

Dr. HEWITT. I do intend to attempt to summarize the rather brief statement that I shall hand in to you. [See p. 404.]

I have been involved in the practice of internal medicine and infectious diseases for over 30 years and regard myself more as a clinical scientist than a laboratory scientist.

My involvement in this field began in 1969, when I was requested by Dr. Van Houweling, of the Bureau of Veterinary Medicine, to evaluate residues of streptomycin in food from animals and poultry as a human health hazard. Although I appear at the request of the Animal Health Institute, I do not consider myself as appearing on anyone's behalf other than my own.

I do not intend to address any of the multitude of statements from various sources concerning penicillin and tetracycline in subtherapeutic amounts in animal feed which could be characterized, depending on one's convictions or interpretations, as biased, pejorative, inaccurate, or self-serving. The simple remedy for this for anyone interested in an informed consideration of this subject or an insightful vote upon H.R. 7285 is the reading of the superbly balanced, critical 3½-page summary of the National Research Council report entitled: "The Effects on Human Health of the Subtherapeutic Use of Antimicrobials in Animal Feeds," which points out that the asserted risks of this use of antimicrobials in animal feeds has neither been proven nor disproven. The inaccuracies in section 2 which are extremely misleading have been commented on adequately by Mr. Rose. I will express some opinion about the deficiencies in the text of the bill and my opinion concerning the counterproductive influence it portends for a reasoned judgmental approach to a primarily medical and scientific problem in a moment.

Any implication that pathogenic bacteria originated in animals causes disease in man for which there is virtually no effective antibiotic therapy is simply totally incorrect other than as a clinical curiosity.

Section 2, paragraph 6, and section 3, paragraph 2(B), constitute significant deficiencies and an oversimplistic solution to the problem of the prevalence of multiple-resistant bacteria in animals, whatever the problem may be. If the bill is intended to serve the broad purpose expressed in section 2(6) and section 3(1), it is clearly possible that other antimicrobials with the same or even greater threats due to bacterial resistance could be substituted based on theoretical considerations or even because a specific agent was not employed for the therapy of disease in man. Since the appearance of specific drug resistance in bacteria is not a one-to-one relationship between the particular drug and resistance to it, there can be no guarantees that the resistance patterns of the bacterial population which would emerge after the use of even a compound which was unique in its chemical classification might differ significantly from those following the use of penicillin or tetracycline.

The problem which H.R. 7285 addresses is clearly complex and is not susceptible to a crisp, precise answer with a reasonable semblance of accuracy. Any acceptable solution will require the most studious and wise blend of facts, reason, and judgment. The opportunity to evaluate the hazard to human health of the subtherapeutic use of antimicrobials in animal feed over a period of 25 years fails, in my view, to justify a 180-day solution. Rather, it suggests a somewhat emotional need to circumvent a reasoned judgmental approach in which whatever political considerations seemed important would also be taken into account.

Neither the Food and Drug Administration nor the National Research Council task force have provided definitive answers as yet to the question with which H.R. 7285 is concerned. I, nonetheless, believe this answer will be forthcoming.

Despite the difficulties in the epidemiologic study of this problem upon which the NRC report has commented the importance of the research should not be underestimated, since the markers of bacterial resistance could identify channels of transmission between animals and man of factors which we have not yet suspected. Furthermore, I have great confidence in the forthrightness, honesty, wisdom and the professional and administrative competence of the present Commissioner of the Food and Drug Administration.

Although the review processes of that agency are often cumbersome, frustrating, and occasionally even marginally acceptable, the principles which they involve are the best we have, and I shall be willing to accept—while reserving the right to object—whatever decision is forthcoming from them, whether I agree with it or not.

As I have sat through this day of testimony, the bottom line, it seems to me always to be human health, and yet I really haven't heard anybody talk about disease in man, although there has been a great deal of discussion about bacteria-bearing plasmids, and how these plasmids in bacteria may be transmitted back and forth between the two ecosystems.

In the few remaining minutes, I would like to do three things: dispel the notion that tetracycline is an important antibiotic for the treatment of life threatening or serious disease in man. Tetracycline is really no longer useful for the treatment of any serious disease in man. And the illusion which Mr. Dingell made that tetracycline is no longer useful for the treatment of cholera simply reflects the fact that tetracycline really is no longer indicated for the treatment of cholera, and indeed antibiotics or antimicrobials are not important for the treatment of the disease since it has been discovered what constitute the life-saving therapy for the particular infection.

Tetracycline is almost everywhere around us. It is extensively used for treatment of acne, and somewhat contrary to the opinions that were expressed, acne in young girls is really a very threatening disease. It is a terribly emotionally upsetting condition and may lead to all kinds of problems later in life, to say nothing of the problems which acne can generate in the skin, requiring plastic surgery and various other sorts of more progressive types of therapy. So although it may be a cosmetic medication, it is, nonetheless, I think, usually indicated.

Interestingly enough, it is not only given extensively, as we found when we were doing a survey on the UCLA campus for urinary tract infection in coeds—10 percent of the girls, or 23,000 to 30,000 student-campus, were at that time on some antibiotic, the majority of which were taking tetracycline for the treatment of acne.

Since that time, tetracycline has become widely available in lotions and ointments as well as even in soap for the management of this disease. Actually, tetracycline is so prevalent in the environment of man that it has been proposed that the archeologists in future times will use tetracycline in the bones of humans as an archeological marker.

Now, the second point that I would like is this alarming statement that has been made that the discovery of new drugs is diminishing and that the discovery of unique compounds is diminishing, I think it is well to point out that you only need one unique compound to result in a whole series of other compounds based upon biochemical engineering.

Take the sulfonamides, for example, discovered sometime back in the 1930's. From the discovery of the active agent, the sulfonamides were the first antibacterial substances and there have been literally hundreds of sulfonamide compounds defined for not only the treatment of ordinary bacterial infections but for the treatment of other infectious diseases, such as leprosy, and even malaria.

Strangely enough, despite the widespread use of sulfonamides in animal feed, and their extensive use in human medicine, they remain the treatment of choice for urinary tract infections in young females with highly successful results.

From the sulfonamide biochemical engineering, other agents were developed, such as diuretic agents, agents for the treatment of gout, and hypertensive compounds, all based on biochemical engineering.

Another example is the literally thousands of compounds which have been developed from the basic structure, which have not only been effective in the treatment of infectious diseases resistant to the penicillins and tetracyclines, but also by means of this biochemical engineering, methods and compounds have been developed which actually are able to get around the varied mechanisms of resistance which are determined by these plasmids.

Another point I would like to make is this matter of the relationship of resistant organisms to the total load of antibiotics that are administered. This is not a straight-line relationship. You might have gotten the impression that as you increase the dose of an antibiotic, in other words, the total dose of antibiotics which is given to the bacterial ecosystem and plot against that the percentage of resistant bacteria, you may have gotten the idea that as you increase this total load of antibiotics, you get a straight-line relationship, and, finally, you are up here where 100 percent of the organisms are resistant to the antibiotics to which you are exposing.

That isn't true at all. You start out here at a very low level and, to be sure, they increase, but then at, say, a certain level, maybe 10 percent, they no longer go up, because there are other bacteria in the ecosystem which keep them in equilibrium, and when the antibiotic is stopped, as somebody pointed out in previous testimony, this incidence of antibiotic-resistant bacteria rather promptly falls.

I have one final point to make which will only take a minute. That is the matter of whether the changing problems of antibiotic therapy and the treatment of serious infections is the result of antibiotic resistance, and there is no question that is one factor, but it really is a factor of lesser importance, and many of the things which doctors are doing in hospitals now are the things which are responsible for the increasing problems and the increased resistance of the infections which we encounter. Things such as respiratory care units, coronary care units, burn centers, dial system units; these are where the problems of resistant infectious disease occur, and it is not only the resistance to the bacteria which we are called upon to treat, but the problems of the host resistance in the patients who have those infections, and I might say that one of the major problems I think of host resistance is related to malnutrition, which is somewhat peripherally concerned in this bill.

Thank you.

[Dr. Hewitt's prepared statement follows:]

STATEMENT OF
WILLIAM L. HEWITT, M.D.
ON H.R. 7285, "ANTIBIOTICS PRESERVATION ACT"
BEFORE THE
SUBCOMMITTEE ON HEALTH AND ENVIRONMENT
OF THE
HOUSE COMMITTEE ON INTERSTATE AND FOREIGN COMMERCE
JUNE 12, 1980

I am William L. Hewitt, M.D., a Professor of Medicine and Chief of the Division of Infectious Diseases at the University of California School of Medicine, Los Angeles. I have been engaged in the practice of Internal Medicine and Infectious Diseases for 30 years and although my bibliography is reasonably extensive as would be anticipated for someone whose career has been in academic medicine I regard myself more as a clinical scientist than a laboratory scientist. My involvement in the relationship of antibiotics in animal feed to human health began in 1969 when I was requested by the then Director of the Bureau of Veterinary Medicine, Dr. C. D. Van Houweling, to evaluate residues of streptomycin in food from animals and poultry as a human health hazard. Although I appear at the request of the Animal Health Institute I do not consider myself as appearing on anyone's behalf other than my own.

I do not intend to address any of the multitude of statements from various sources concerning penicillin and tetracycline in subtherapeutic amounts in animal feed which could be characterized, depending on one's convictions or interpretations, as biased, pejorative, inaccurate, or self-serving. The simple remedy for this for anyone interested in an informed consideration of this subject or an insightful vote upon HR7285 is the reading of the superbly balanced, critical 3½-page summary of the National Research Council Report entitled The Effects on Human Health of the Subtherapeutic Use of Antimicrobials in Animal Feeds, which points out that the asserted risks of this use of antimicrobials in animal feeds has neither been proven nor disproven. Ill-supported claims will quickly be cast into their proper scientific perspective by an understanding of this easily readable, remarkably clear synthesis of the present state of knowledge and controversy which characterize this public health area.

My present purpose is to comment first upon several inaccuracies and deficiencies in the text of HR7285 and second to express my opinion concerning the counterproductive influence it portends for a reasoned judgmental approach to a primarily medical and scientific problem.

Sec 2(2)(3) are extremely misleading. It is quite basic to understand that the oral administration of antibiotics in subtherapeutic or therapeutic doses has not resulted in the development of multi-resistant pathogenic bacteria in animals or man. These bacteria have been there all the time at least in the context of recent evolution. The discovery of an index agent to which the susceptibility or resistance of a particular type of bacteria can be defined simply provides us with a characteristic which can be recognized and tested for. Such a discovery provides the mechanism for applying a selective pressure upon a bacterial population within which the resistant members have a survival advantage and may become more prevalent. The only pathogenic bacteria in which multiple antibiotic resistance has been substantial and which are transmitted from animals to man resulting in disease are the Salmonella. This may occur without evidence of disease. If symptomatic disease results from animal-to-human transmission (or from human-to-human transmission) the vast majority of cases are a self-limited gastroenteritis which does not require antibiotic therapy and which may even be disadvantagenous. The appropriate antimicrobial management of the cases of salmonellosis which require such therapy is not now, has never been (in the last 20 years) and, in my opinion, is unlikely to be a problem in the foreseeable future. Diseases such as meningitis and gonorrhea are never transmitted from animals to man and any implication that pathogenic bacteria originating in animals cause disease in man for which there is virtually no effective antibiotic therapy is simply totally incorrect other than as a clinical curiosity.

Section 2(4)(5) are extremely vague and would be considerably more compelling if it had been possible for the Office of Technology Assessment Report to define even arbitrarily what they regarded as a "health risk to humans" and to provide even suggestive evidence that the restriction of antibiotics in Western European countries had resulted either in lowered total use or a benefit to human health.

Section 2(6) and Section 3(2)(B) constitute significant deficiencies and an oversimplistic solution to the problem of the prevalance of multiple resistant bacteria in animals whatever the problem may be. If the bill is intended to serve the broad purpose expressed in Sec 2(6) and Sec 3(1) it is clearly possible that other antimicrobials with the same or even greater threats due to bacterial resistance could be substituted based on theoretical considerations or even because a specific agent was not employed for the therapy of disease in man. Since the appearance of specific drug resistance in bacteria is not a one-to-one relationship between the particular drug and resistance to it, there can be no guarantees that the resistance patterns of the bacterial population which would emerge after the use of even a compound which was unique in its chemical classification might differ significantly from those following the use of penicillin or tetracycline.

The problem which HR7285 addresses is clearly complex and is not susceptible to a crisp, precise answer with a rasonable semblance of accuracy. Any acceptable solution will require the most studious and wise blend of facts, reason, and judgment. Social needs with foundations in science or medicine may sometimes be sufficiently pressing that political or legislative solutions are necessary. The opportunity to evaluate the hazard to human health of the subtherapeutic use of antimicrobials in animal feed over a period of 25 years fails in my view to justify a 180-day solution. Rather it suggests a somewhat emotional need to circumvent a reasoned judgmental approach in which whatever political considerations seemed important would also be taken into account. Neither the Food and Drug Administration or the National Research Council Task Force have provided definitive answer as yet to the question with which HR7285 is concerned. I, nonetheless, believe this answer will be forthcoming. Despite the difficulties in the epidemiologic study of this problem upon which the NRC Report has commented the importance of the research should not be underestimated since the markers of bacterial resistance could identify channels of transmission between animals and man of factors which we have not yet suspected. Furthermore, I have great confidence in the forthrightness, honesty, wisdom and the professional and administrative competence of the present Commissioner of the Food and Drug Administration. Although the review processes of that agency are often cumbersome, frustrating, and occasionally even marginally acceptable the principles which they involve are the best we have and I shall be willing to accept (while reserving the right to object) whatever decision is forthcoming from them whether I agree with it or not. In fact, were I told by the present Commissioner of the FDA that he wished to promulgate a regulation referable to these antibiotics within 180 days based upon his thorough evaluation of the problem and did not have the authority to do so I would endorse this bill.

William L. Hewitt, M.D.
Professor of Medicine and Chief
Division of Infectious Diseases
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Los Angeles, California 90024

STATEMENT OF EUGENE LAMBERT

Mr. LAMBERT. Mr. Chairman, I am Eugene Lambert and partner in the Washington, D.C., law firm of Covington and Burling.

For the past 15 years, I have served as counsel to the Animal Health Institute, and it is on their behalf I appear today as a legal thorn in a lovely garland of scientists.

My prepared statement has been submitted to the record, and I intend to summarize it. [See p. 414.]

Mr. Chairman, by your leave, we would like the opportunity, if we could, to submit additional statements for the record on the basis of the testimony that we have heard here today and the testimony of the Government witnesses that has not yet been presented.

Mr. WAXMAN. Without objection, the record will be kept open for—how long do you need?

Mr. LAMBERT. If we could have a few weeks after the Government witnesses have testified, that would be satisfactory.

Mr. WAXMAN. We are planning to hold additional hearings, and we will hold the record open for 10 days after the next hearing for additional comments anyone wishes to submit.

Mr. LAMBERT. We appreciate that.

The Animal Health Institute is a national trade association whose members produce and distribute over 90 percent of the veterinary pharmaceuticals, biologicals, animal pesticides and animal drugs incorporated in animal feed sold within the United States. I apologize that our chairman, Hilmer Jones, doctor of veterinary medicine, is presently attending a conference on veterinary biologics and could not be here.

The testimony of Dr. Hewitt and others certainly made clear we have a decade-long and still-unresolved controversy over many of the scientific issues presented in the so-called subtherapeutic use of animal drugs in feed, where those antibiotics have important human uses as well.

AHI is not here to suggest a scientific solution to that issue, but we oppose the enactment of H.R. 7285 because we believe it represents both unnecessary and inappropriate legislation. The Federal Food, Drug, and Cosmetic Act provides an existing comprehensive mechanism for the regulation of drugs added to animal feeds. This is called the animal drug amendment to the act, enacted in 1968.

Under these provisions it is unlawful to market any new animal drug other than in accordance with the approval of the drug by the Food and Drug Administration.

In addition, the use of that drug in feed by feed mills, or by animal handlers, is subject to additional FDA approvals.

The act requires that the manufacturer demonstrate both the safety and the efficacy of the new animal drug. The act specifically provides the term "safe" has reference to the health of man or animal. Thus, in approving a new animal drug, FDA must specifically find that the use of the drug is safe with respect to the health of man as well as the animals to which the drug is to be administered.

Moreover, FDA is empowered to revoke that approval if it finds that new evidence evaluated, together with the evidence available when the drug was initially approved, shows that the drug is no longer shown to be safe.

Where the Secretary of Health and Human Services finds there is imminent hazard to the health of man, he may withdraw the new animal drug approval in advance of any further administrative proceeding.

Congress has thus provided a comprehensive mechanism and authority under the act to take into account human health as a controlling factor in both the approval and disapproval of new animal drugs, and has given the Secretary nondelegable authority to suspend new animal drug approvals in the event of an imminent hazard to the health of man.

The Animal Health Institute participated directly and supported the passage of the animal drug amendments in 1968 to the act and the controls they provide, assuring that the use of drugs in animals and in animal feeds is safe to the health of man.

This existing authority alone, we submit, is adequate justification for opposing the passage of H.R. 7285.

However, we believe that H.R. 7285 also represents the inappropriate exercise of congressional authority because it entails congressional intervention in a proceeding already begun by FDA to resolve the scientific issues addressed in the bill.

FDA, by notices of opportunity for hearing published in August and October 1977, and with respect to penicillin and tetracycline, has already begun the process provided by the existing statute for restricting the uses of these previously approved drugs.

The companies involved have responded to that proposal by demanding a hearing, and FDA, in a notice published a year later, indicated its willingness and intention to hold that hearing.

Considerable FDA expertise and manpower are already at work on the issues raised by the use of so-called subtherapeutic levels of antibiotics in animal feeds. The personnel involved in these matters are those in the Bureau of Veterinary Medicine and Foods, to whom the Commissioner has assigned responsibility for evaluating the public health risks of the low-level use of antibiotics in animal feed.

The proposed legislation would direct yet a third FDA operating unit, the Bureau of Drugs, to undertake essentially a separate but identical review and determination of these same issues in order to advise the Commissioner in issuing regulations under section 507 of the act, as it would be amended by the bill. This would present problems of prejudgment on the part of the Commissioner in passing on rulemaking required by the bill, and thus could potentially compromise the hearing process FDA has begun under existing statutory authority.

As I am sure this committee is aware, funds have been appropriated to permit FDA to undertake research designed to answer some of the questions posed by the so-called subtherapeutic use of antibiotics in animal feed. FDA has, in effect, been requested by the Senate and House Appropriations Committees not to complete the pending proceedings until the results of that research are available to be evaluated. We believe that this judgment of the House and Senate Appropriations Committees should be respected, and the parallel authority should not be set up to reach decisions without the safeguards of existing law and without the benefits of the research to be conducted by FDA.

Where existing authority and procedures are adequate, the Animal Health Institute has uniformly opposed passage by Congress of the legislation directed to controlling specific animal drugs. We believe that congressional reliance on existing authority and oversight on that exercise of that authority represents a sound approach to government.

That is the situation we believe presently exists with respect to the regulation of low-level use of antibiotics in animal feed, and it is for this reason that AHI opposes H.R. 7285 as unnecessary and unwise.

I would be happy to answer any questions you have.

Thank you.

[Mr. Lambert's prepared statement follows:]

STATEMENT OF THE ANIMAL HEALTH INSTITUTE ON H.R. 7285, "ANTIBIOTICS PRESERVATION ACT" BEFORE THE SUBCOMMITTEE ON HEALTH AND ENVIRONMENT OF THE HOUSE COMMITTEE ON INTERSTATE AND FOREIGN COMMERCE

JUNE 12, 1980

My name is Eugene Lambert, and I am a partner in the Washington, D.C. law firm of Covington & Burling. For the past fifteen years, I have served as counsel to the Animal Health Institute ("AHI") and it is on AHI's behalf that I appear today.

The Animal Health Institute is a national trade association whose members manufacture and distribute over 90% of the veterinary pharmaceuticals, biologicals, animal pesticides and animal drugs incorporated in animal feed sold within the United States. AHI members include companies that manufacture all of the presently-approved antibiotics used in animal feed, including both those that would be covered by H.R. 7285, and those which the Food and Drug Administration ("FDA") has identified as substitutes.

The testimony of Dr. Hewitt and others makes evident the decade's long and still unresolved controversy over the scientific issues presented in the so-called "subtherapeutic" use of antibiotics in animal feed where those antibiotics also have important uses in human medicine. AHI can not, of course, suggest a scientific resolution of those issues and the propriety of these uses of tetracyclines, penicillin, and other specific human-use antibiotics is being addressed in appropriate forums by the manufacturers of those drugs.

It is the position of the Animal Health Institute, however, that enactment of H.R. 7285 represents an unnecessary and inappropriate legislative intrusion into an existing fully adequate regulatory system that FDA is already implementing. For these reasons, AHI opposes the enactment of H.R. 7285.

The Federal Food, Drug, and Cosmetic Act ("the Act") provides a comprehensive mechanism for the regulation of drugs added to animal feeds. That mechanism is contained in a coalescence of three areas of FDA authority, covering drugs, antibiotics, and food additives, called the

Animal Drug Amendments to the Act. Enacted in 1968, following lengthy hearings and debate, the Animal Drug Amendments comprise principally Section 512 of the Act. (21 U.S.C. 360b). Under these provisions, it is unlawful to market any new animal drug other than in accordance with the approval of the drug by the Food and Drug Administration. Furthermore, the use of the drug by feed mills and livestock handlers must also be in accordance with additional FDA approvals.

The Act requires that the manufacturer demonstrate both the safety and the efficacy of the new animal drug, and the Act specifically provides that "The term 'safe'. . . has reference to the health of man or animal." Section 201(u). Thus, in approving new animal drugs, the Commissioner must specifically find that the use of the drug is safe with respect to the health of man as well as the animals to which the drug is to be administered. The Act also prescribes stringent tests to be met by the applicant in demonstrating the safety of the drug to man or animals. See Sections 512(d)(1)(A), (B), and (2). Moreover, FDA is empowered to revoke the approval if it finds that "new evidence ... evaluated together with evidence available...when the application was approved, shows that such drug is not shown to be safe for use. . ." Section 512(e)(1)(B).

Normally, FDA is required to provide notice and opportunity for hearing before revoking an approval for any new animal drug. See Section 512(e)(1). Where the Secretary of Health and Human Services "finds that there is an imminent hazard to health of man", the Secretary (who may not delegate this authority to FDA) may withdraw a new animal drug approval in advance of an FDA hearing. Section 512(e)(1).

Congress has thus provided comprehensive authority under the Act to take into account human health as a controlling factor in both the approval and disapproval of new animal drugs, and has given the Secretary non-delegable authority to suspend new animal drug approvals in the event of an imminent hazard to the health of man. Under these circumstances, we believe that the proposed legislation adds simply a superfluous layer of regulatory activity to FDA's already abundant authority to control the use of antibiotics based on any purported hazard to the health of man resulting from use of these drugs in animal feed. The existing authority alone, we submit, is adequate justification for opposing the passage of H.R. 7285.

We believe, moreover, that H.R. 7285 represents the inappropriate exercise of Congressional authority for another reason, because it entails Congressional intervention in a proceeding already begun by FDA to resolve the scientific issues addressed by H.R. 7285.

FDA, by notices of opportunity for hearing published in the Federal Register on August 30, 1977 (42 Fed. Reg. 43772) and October 21, 1977 (42 Fed. Reg. 56264), has already begun the process provided by the existing statute for restricting the uses of these previously approved drugs. The companies involved have responded to that proposal by demanding a hearing, and FDA has indicated its willingness and intention to hold a hearing. See 43 Fed. Reg. 53827 (November 17, 1978). The Appropriations Committees of Congress have, however, directed FDA to conduct certain basic research before any final action is taken in this adjudicatory proceeding. See H.R. Rep. No. 96-242, 96th Cong., 1st Sess. at 101 (1979) and S. Rep. No. 96-246, 96th Cong., 1st Sess. at 100 (1979) on H.R. 4387, 96th Cong., 1st Sess. (1979). We believe it is particularly inappropriate to contemplate legislation that would initiate new regulatory procedures while these responses to previous Congressional mandates are pending and statutory proceedings are underway with the objective of resolving the very scientific issues H.R. 7285 seeks to address.

Considerable FDA expertise and manpower are now at work on the issues raised by the use of low levels of antibiotics in animal feeds. The personnel involved in these matters are those in the Bureaus of Veterinary Medicine and Foods, to whom the Commissioner has assigned responsibility for evaluating the public health risks of the low level use of antibiotics in animal feed. The proposed legislation would direct a third FDA operating unit, the Bureau of Drugs, to undertake essentially a separate, but identical, review and determination of these issues in order to advise the Commissioner in issuing regulations under Section 507 of the Act, as it would be amended by H.R. 7285. This could present problems of prejudgment on the part of the Commissioner in passing on rulemaking required by H.R. 7285, and thus potentially compromise the hearing process that FDA has begun under existing statutory authority.

As this Committee is aware, funds have been appropriated to permit FDA to undertake research designed to answer some of the questions posed by the so-called subtherapeutic use of antibiotics in animal feed. FDA has in effect been directed not to complete the pending proceedings until the results of that research are available to be evaluated in the proceedings. We believe that this judgment of the House and Senate Appropriations Committees should be respected, and that parallel authority should not be set up that could reach decisions without the safeguards of existing law and without the benefits of the research to be conducted by FDA.

Where existing authority and procedures are adequate, AHI has uniformly opposed the passage by Congress of legislation directed to controlling a specific animal drug. We believe that Congressional reliance on existing authority, and oversight on the exercise of that authority represents a sound approach to government. That is the situation that presently exists with respect to the regulation of the low-level use of antibiotics in animal feed, and it is for this reason that AHI opposes H.R. 7285 as unnecessary and unwise.

I would be happy to answer any questions that the Committee may have concerning the position of the Institute.

Mr. **Waxman**. Thank you very much for your testimony.

It seems to me that what you have said, and what some other witnesses on this panel also have echoed, is that the Food and Drug Administration has the legal authority to act, and they are the appropriate ones to look at the scientific evidence and to make a determination of whether there is reason for the Government to be involved in any way in the restriction of use of antibiotics for subtherapeutic use in animals.

Do we have conclusive evidence that antibiotics at subtherapeutic levels in animal feeds promote growth and feed efficiency? Do we know it does good for the animals?

Dr. **Visek**. I would say, I think I could probably quote around 900 scientific papers that have addressed the subject, and the majority show that there is a benefit under practical conditions.

Mr. **Waxman**. If we had a computer printout of those 900 reports, would it extend the equivalent of Mr. Dingell's printout? Perhaps?

Dr. **Visek**. Perhaps.

Mr. **Waxman**. What about the alternatives? What would be the economic impact?

Dr. **Visek**. There is a difference of opinion as to what the economic impact would be. It might, in fact, be greater than our laboratory evidence shows. Remember, many of the experiments done in experiment stations over the country are done in laboratories quite clean compared to the practical conditions under which livestock are produced.

There are situations where in veal/calf operations, for instance, you might lose half your animals without antibiotics; that has been shown.

Some people feel——

Mr. **Waxman**. Excuse me. I want to interrupt you to say it was my understanding that Mr. Dingell wouldn't prohibit the use of antibiotics in surgery or for therapy for animals. He would restrict the subtherapeutic dosage, the dosage that would not be used for therapy at all, but, as a preventative measure.

Dr. **Visek**. Part of the reasons you use antibiotics is to control diarrhea and shipping fever in livestock, for instance, that moves in interstate commerce. One of the problems with young animals, and particularly beef cattle entering the feedlot is that they have been transported in this country perhaps from Florida to South Dakota at freezing temperatures or considerably lower. They come to strange quarters, and fail to eat. The quicker they get on feed, the better. One of the things that antibiotics do in feed is to facilitate this adoption process which is very significant in preventing disease.

You alluded to the possible therapeutic use of antibiotics in the veal/calf operation where the dosages used are dosages higher than you use as subtherapeutic or growth promoting dosages. Nevertheless it has been shown in cattle feeding, that the feeding of as little as 10 parts per million of chlortetracycline reduces liver abscesses and helps get the animal on feed quicker.

It is hard to say what the economic impact would be if these antibiotics could not be used in this way. This may vary as a consequence of climatic and other conditions. In a bad winter such as we have had in the corn belt in recent years losses might be considerably greater than they might be in another year.

Mr. **Waxman**. What would be the alternative to use of antibiotics?

Dr. **Visek**. We have no alternatives in some of the situations that I alluded to, because the alternatives such as sulfonamides and nitrofurans and other antibiotics are under scrutiny and may, in fact, be removed from use. In the case of an anaplasmosis in cattle, there is no substitute. Liver abscesses in cattle are not well controlled by other agents, so in some instances we have no alternative at the moment.

Mr. **Waxman**. A recent article by the feed division of the Missouri Farmers Association stated that when efficacy of subtherapeutic levels of antibiotics was tested against a controlled group of nonmedicated pigs from well-managed commercial facilities, there was no significant difference in overall weight gain.

They go on to state, "If economics were applied to this trial, pigs fed nonmedicated rations would be the most profitable." It seems to me this says the efficacy of feed additives only appears in poorly managed feedlots, and I would like to know what you have to say about that, and aren't we encouraging poor animal management by our dependence on subtherapeutic——

Dr. **Edds**. As I said to your contact when I came, we have run similar trials using another growth proponent, arsenetic acid and it was pointed out, under our "laboratory conditions", under well-managed swine operations, which evidently this one pertains to, the floors are cleaned daily, the animals are well kept, well managed, probably shades are provided, the ideal conditions; so you don't get the same degree of growth stimulation there as you do under farm conditions.

And I think our experiments have to be looked at with that bias in mind, that we are not getting the farm conditions, but we are getting a laboratory condition.

Dr. **Visek**. Mr. Waxman, I didn't answer an earlier question you asked. First of all, the economic issue, I think, will be addressed in subsequent testimony before this committee. I am not an economist, and I don't really know how to assess the economic impact. I have seen figures of former years where we were talking somewhere in the order of $2 to $4 billion in 1975 or 1976, but those conditions do not apply today.

The other thing I think we must recognize is that the ideal laboratory or the ideal production unit is not as common as we think. There are lots of small producers, hundreds of thousands of them in the United States, that don't have optimum conditions for production, but yet they contribute a significant amount of meat to our food supply.

Mr. **Waxman**. The theory that has been advanced is that the pool of bacteria that would be resistant to antibiotics would be increased by the use of antibiotics. Have you found that to be the case in animals? Do you think that the use of medicated feeds can predispose animals to disease because they have developed immunity? Have you seen evidence of that?

Dr. **Edds**. Could I speak to that? I would like to get my testimony before you before I have to leave.

We have run trials, as they have at the University of Virginia for years, where we are feeding dried manure from the cattle back to the cattle. Ten percent of their ration is their own manure, and we have done this for the past 3 years, and this feed contains antibiotics. I thought when we started the trial that we would accumulate antibiotics into a cumulative resistant population, but we did not. The animals, as far as carcass quality, are as good today as 3 years ago in the animals we have produced over this 3-year period.

Mr. **Waxman**. You don't think the period of time might not be too short?

Dr. **Edds**. All I can report is 3 years. We are continuing this trial.

Mr. **Waxman**. I want to thank all of you for your testimony, and I recognize Dr. Carter for questions.

Mr. **Carter**. Thank you, Mr. Chairman, and Dr. Hewitt, we have been here since 10:30 this morning, and I would like you to present a certificate to me that I am entitled to 4½ hours of continuing education.

Dr. **Hewitt**. I will sign yours, Dr. Carter, if you will sign mine.

Mr. **Carter**. I will be happy to do it. I believe you are a professor of the University of California?

Dr. **Hewitt**. It doesn't make any difference.

Mr. **Carter**. So, OK, I will sign yours. Thank you, sir.

It has been very interesting to hear you gentlemen discuss these things, I think so very intelligently, and I want to commend you on what you have said.

I have seen no one concerning this legislation previous to this day except my counsel who works for me, and that has been it. We have had to get a knowledge of what legislation is coming before us, but what I have said today has been absolutely unbiased, and from what I know of this legislation, I would say why use this. Is it economic? Is it the question of the economics of it? Using the legal term, res ipsa loquitur, the thing speaks for itself; nobody is going to use it if it isn't effective, it seems to me, for calves or for piglets, or for anyone else, and it has not been proved that it is going to produce an andromeda strain or any other strain that would adversely affect us and cause a bubonic plague, like the swine flu was supposed to cause a few years ago.

I want to thank this distinguished panel, and whether I get that certificate or not, I am thankful for the education I have received.

Thank you very much.

Mr. **Waxman**. Mr. Dannemeyer?

Mr. **Dannemeyer**. I have a question of Dr. Hewitt. One of the things that bothers me about this subject is evidence of approximate cause, I suppose, is a way to express it. And supposing you have some chickens that you feed antibiotics to, such as penicillin or tetracycline, does the antibiotic get into the meat of the chicken?

Dr. **Hewitt**. All of these agents that we are discussing, at least the penicillins and tetracyclines are all absorbed when given by mouth, so I am confident that you would be able to recover these antibiotics from the urine, let's say, of the animal or poultry to which they are administered in no matter what amounts, even the very small subtherapeutic amounts. These would obviously be small concentrations because the animal is only getting an excessively small dose.

Mr. **Dannemeyer.** Would you find it in the meat of the chicken?

Dr. **Hewitt.** I have no doubt if there were sufficiently sensitive methods employed, you could find it in the meat of the chicken.

Mr. **Dannemeyer.** Supposing we had some of those antibiotics in the meat of the chicken and a human comes along and eats the meat? What happens to the human system when the human eats that meat?

Dr. **Hewitt.** That was the subject, really, of my introduction to this whole subject. It had to do with the use of streptomycin, which is usually not absorbed, but even assuming that it was absorbed in its entirety, you would have to eat something like 50 chickens in a day or a week in order to get anything like you would get from taking, say, a 200-milligram capsule of tetracycline.

Now, the Department of Agriculture, of course, has very good regulations on what are termed withdrawal periods before these animals or poultry can be killed, and you should certainly all know, as I am sure you do, that the duration with which these antibiotics are in an animal are really very short, indeed. A dose of penicillin, half of it is excreted within half an hour, and usually after 24 hours you will not be able—in fact, even a shorter time than that, you won't be able to demonstrate any drug in the bloodstream at all, so when you combined the matter of excessively small doses, very prompt elimination, and then the withdrawal periods that have been prescribed by regulatory process, you know, the likelihood of your getting any significant amount, if any at all, of these antibiotics is really very remote, indeed.

Mr. **Dannemeyer.** Let's assume, for the sake of argument—giving the proponents of this legislation their due—that there was an unusual chicken, or something, and a human ate a piece of chicken with a lot of that antibiotic in it, what would the human system do with the antibiotic in the digestive system?

Dr. **Hewitt.** It would do exactly what is done when all of us get those same antibiotics; it would be absorbed, and it would be promptly excreted.

Mr. **Dannemeyer.** People are contending, I think, that some of the antibiotics are going to establish a resistance in the human system to the use of the antibiotics in the future. Therefore, we should prohibit the use in animals?

Dr. **Hewitt.** Excuse me, Mr. Dannemeyer, I really don't think the proponents of the bill are suggesting that. I think they are not. I think they recognize this very, very remote possibility that one would ingest antibiotics by ingesting an animal which had gotten these small amounts.

What they are suggesting, and what we know to occur, as a matter of fact, is that the bacteria which have become resistant in the animal as a result of their exposure to the antibiotics are transmitted to man. I really don't think that the proponents of the bill are concerned about getting antibiotics out of the food system.

Mr. **Waxman.** If the gentleman would yield, I at first was under the same misapprehension that perhaps there was a similar kind of case to a residue that remains in the meat that then is transmitted and ingested. But earlier testimony indicated that the concern was that there is a bacteria pool, and in that bacteria pool that some of that bacteria develops immunity to an antibiotic and that becomes transmitted because there is a transfer back and forth between all living beings of this bacteria pool.

There was a suggestion that there is some part of the bacteria pool that is not so transferable. There is a question of whether, in fact, even though there is an acknowledged transfer of some of that pool, whether that would, in fact, transfer to a human, the immunity developed in the animal, and also become immunized to a pool of bacteria in human beings.

Mr. **Carter.** We might develop a strain of bacteria which would be resistant to penicillin or Terramycin; we might develop a strain of one of these particular germs.

Mr. **Dannemeyer.** I suppose there is a possibility such a thing can be developed.

Dr. **Hewitt.** The organism we are talking about most in this context, the name of the salmonella, and the incidence of salmonellosis in man in this country is certainly a major public health problem, but, nonetheless, the mortality from salmonellosis is very, very low indeed. Of all the thousands of cases, I think the mortality per year is something like 60 or 70 people in this entire country.

These organisms, if they cause disease at all, cause disease which normally is controlled by our normal host defenses if we are well. The areas where salmonellosis causes a problem are in areas where nutrition is poor, and where poverty exists, and where these people don't have the natural host defenses that we have in this country, and that is why really antibiotics resistance among the salmonella doesn't constitute a serious problem, because most of them don't need to be treated anyway.

You take fluids, and maybe some paregoric, or lomotil, something of this sort, or Peptobismol now is a popular agent, and you bring this under control with your own host defenses.

Mr. **Dannemeyer.** How long has the cattle industry, for instance, been feeding antibiotics to cattle, chickens, and things like this?

Dr. **Hewitt.** I would think 20 years.

Mr. **Lambert.** Over a quarter of a century. The initial approvals were around 1950 or shortly thereabouts.

Mr. **Dannemeyer.** I guess the proponents would say we must not foreclose the possibility that human harm will come about through the evolution of time, the length of which we know not. Is that what they are saying? It hasn't happened in 25 years, but we must guard against the possibility that at the end of 50 years it will be with us. Is that what they are saying?

Mr. **Lambert.** I think I better not try to put the words in the mouth of the proponents.

Mr. **Waxman.** This is not the group to ask that question.

Just another one or two very quick questions of Dr. Hewitt. It seems what was being argued was that the bacteria that is antibiotic resistant would require a more potent antibiotic with potential side effect. Do you see any validity of that argument?

Dr. **Hewitt.** I think there is some truth to that. For example, there will be certain resistant bacteria in which other agents will be required, which might have more potential for toxicity than the index agent that you are talking about.

On the other hand, there are also agents of the same generic group, let's say, among the sulfoniums, which, by virtue of their chemical configuration get around this particular mechanism of resistance, so this agent is still safe and the same class as the original one to which the organism is resistant may then be effective against this particular resistant organism. That is what I referred to about the ingenuity of the biochemical engineering process that is now underway.

Mr. **Waxman**. While we are not addressing the concern about residues in meats that can be ingested by people, isn't there some requirement that animals being slaughtered have to be held several days during which period of time antibiotics cannot be administered?

Mr. **Lambert**. It depends on the specific agent. To get an approval for a drug to be used in animal feed, the manufacturer must present studies which show the speed with which the agent depletes from not only the blood and urine, but also the meat of the animal, and those studies then determine the withdrawal period that is required.

In addition, safety studies must be presented with respect to human safety, of the residues, if there are any, and those also enter into the length of the withdrawal period. So it varies completely by the agents and the data presented to FDA.

Mr. **Waxman**. We are talking about a relatively short period of time under scientific consensus of disposal of the body by any antibiotics used; that is really not an issue. Is that correct?

Mr. **Lambert**. That is correct. It is relatively short. Well, the sulfonamides, I believe are now somewhere between 2 weeks and 1 month for some of them, as withdrawal time, and other antibiotics are very brief periods of time. So it varies.

Mr. **Waxman**. I want to thank you both for your testimony today. I think all of us should receive a certificate on our continuing education.

Thank you.

[Whereupon, at 4:15 p.m., the subcommittee adjourned, to reconvene subject to the call of the Chair.]

ANTIBIOTICS IN ANIMAL FEED

TUESDAY, JUNE 24, 1980

House of Representatives,
Subcommittee on Health and the Environment,
Committee on Interstate and Foreign Commerce,
Washington, D.C.

The subcommittee met, pursuant to notice, at 10 a.m., in room 2218, Rayburn House Office Building, Hon. Henry A. Waxman, chairman, presiding.

Mr. Waxman. We will come to order.

This is a continuation of our hearing on the bill, H.R. 7285. I would like to call forward the witnesses that we have to testify before us today together, as a panel: Lester M. Crawford, Director, Bureau of Veterinary Medicine, Food and Drug Administration; Carol Tucker Foreman, Assistant Secretary for Food and Consumer Services, U.S. Department of Agriculture; and Howard Hjort, Director, Economics, Policy Analysis and Budget, U.S. Department of Agriculture.

Dr. Crawford.

STATEMENTS OF LESTER M. CRAWFORD, D.V.M., PH. D., DIRECTOR, BUREAU OF VETERINARY MEDICINE, FOOD AND DRUG ADMINISTRATION, PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH AND HUMAN SERVICES; CAROL TUCKER FOREMAN, ASSISTANT SECRETARY FOR FOOD AND CONSUMER SERVICES, DEPARTMENT OF AGRICULTURE; AND HOWARD W. HJORT, DIRECTOR, ECONOMICS, POLICY ANALYSIS AND BUDGET

Dr. Crawford. Mr. Chairman, I would like to read a portion of the testimony and enter the rest in the record. [See p. 425.]

Mr. Waxman. Without objection, the full text of all the testimony offered by our witnesses today will be made part of the record, and each of you can proceed in any way you wish.

Dr. Crawford. The Bureau of Veterinary Medicine has been concerned for some time about the extent of the health hazard posed by the use of antibiotics in animal feed. We have been particularly concerned about the long-term, low-level, nontherapeutic use, that is, used for improving feed efficiency, rate of weight gain, and disease prevention.

We are concerned because these uses promote the development of drug-resistant bacteria in animals, because routes for the transfer of these resistant bacteria to man are available, and because drug resistance can be transferred to bacteria that cause human diseases. There is, therefore, the potential for compromise of human drug therapy.

The Bureau's belief that the continued unrestricted subtherapeutic use of the antibiotics presents risks to human and animal health is based upon consideration of a number of factors:

(a) Long-term, low-level feeding of antibiotics to animals promotes by natural selection from the pool of normal intestinal flora those enteric—gut—bacteria—primarily *E. coli*—that contain R-plasmids. R-plasmids, also known as R-factors, are extra chromosomal genetic material which confer antibiotic resistance to host bacteria. These plasmids can be transferred between various kinds of bacteria through cell-to-cell contact—conjugation.

Simultaneous resistance to several unrelated antibiotics is commonly carried on a single plasmid and therefore is simultaneously transferred from one bacterium to another.

(b) *E. coli* strains bearing R-plasmids can be transferrd from animal to man. Under the proper circumstances, organisms of animal origin can colonize in the the human gut. However, colonization is not considered necessary for transfer of drug resistance to strains that inhabit the human gut.

(c) Use of antibiotics also causes selection for pathogenicity factors, that is, disease-causing factors. These factors and drug resistance have been shown to be linked on the same plasmid. Pathogenicity and antibiotic resistance can therefore be transferred simultaneously to other organisms.

(d) R-plasmids can be transferred from normally nonpathogenic *E. coli* to certain pathogenic strains of bacteria with which they may come in contact in man or animals. Since R-plasmids carry drug resistance, this transfer can result in the creation of pathogenic strains of bacteria which are resistant to antibiotic therapy.

For these reasons, the Food and Drug Administration has since 1977 attempted to restrict the use of penicillin and tetracycline in low-level amounts in animal feeds.

Thank you.

[Testimony resumes on p. 501.]

[Dr. Crawford's prepared statement and attachment follow:]

STA

LESTER M. CRAWFORD

DIRECTOR

BUREAU OF VETERINARY MEDICINE

FOOD AND DRUG ADMINISTRATION

PUBLIC HEALTH SERVICE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. Chairman:

I welcome this opportunity to discuss with you and the Subcommittee the views of the Bureau of Veterinary Medicine, Food and Drug Administration (FDA), on the bill H.R. 7285 regarding the use of antibiotics in animal feeds.

Before offering specific comments on this bill, let me first discuss why the Bureau is concerned about the continuous use of low levels of antibiotics in animal feeds; our activities in this important area; and the recent National Academy of Sciences (NAS) report. To supplement my testimony, I would like to submit for the record several documents that are relevant to this issue. A list of these documents is attached to my statement.

THE PUBLIC HEALTH CONCERN

The Bureau of Veterinary Medicine has been concerned for some time about the extent of the health hazard posed by the use of antibiotics in animal feed. We have been particularly concerned about the long-term, low-level, nontherapeutic use, that is, use for improving feed efficiency, rate of weight gain, and disease prevention. We are concerned because these uses promote the development of drug resistant bacteria in animals; because routes for the transfer of these resistant bacteria to man are available; and because drug resistance can be transferred to bacteria that cause human diseases. There is, therfore, the potential for compromise of human drug therapy.

In late 1977 and early 1978, the Bureau of Veterinary Medicine published in the Federal Register proposals to restrict the addition to animal feed of low levels of certain antibiotic drugs. These drugs are penicillin, two tetracycline drugs (oxytetracycline and chlortetracycline), and combination products containing these antibiotics. Penicillin and the tetracyclines were chosen as the initial subjects of regulation because of the extent of their use in animal feeds and their importance in the treatment of human disease.

The Bureau's belief that the continued unrestricted subtherapeutic use of the antibiotics presents risks to human and animal health is based upon consideration of a number of factors:

-- Long-term, low-level feeding of antibiotics to animals promotes, by natural selection from the pool of normal intestinal flora, those enteric (gut) bacteria (primarily *E. coli*) that contain R-plasmids. R-plasmids, also known as R-factors, are extra chromosomal genetic material which confer antibiotic resistance to host bacteria. These plasmids can be transferred between various kinds of bacteria through cell-to-cell contact (conjugation). Simultaneous resistance to several unrelated antibiotics is commonly carried on a single plasmid and therefore is simultaneously transferred from one bacterium to another.

-- E. coli strains bearing R-plasmids can be transferred from animal to man. Under the proper circumstances, organisms of animal origin can colonize in the human gut. However, colonization is not considered necessary for transfer of drug resistance to strans that inhabit the human gut.

-- Use of antibiotics also causes selection for pathogenicity factors, that is, disease-causing factors. These factors and drug resistance have been shown to be linked on the same plasmid. Pathogenicity and antibiotic resistance can therefore be transferred simultaneously to other organisms.

-- R-plasmids can be transferred from normally nonpathogenic E. coli to certain pathogenic strains of bacteria with which they may come in contact in man or animals. Since R-plasmids carry drug resistance, this transfer can result in the creation of pathogenic strains of bacteria which are resistant to antibiotic therapy.

Interpretation of research and epidemiological data leads more to the conclusion that the foregoing series of events is real rather than potential. It is certain that the resistant pathogens occur as a result of R-plasmid transfer, and the pool of resistant pathogens is further increased by subsequent antibiotic use.

Continued unrestricted subtherapeutic use of antibiotics in animal feed will increase the pool of drug-resistant bacteria in our environment. Moreover, the prospect of pathogens becoming drug resistant is considered a real threat to human health. This is demonstrated by the recent emergence of human diseases (e.g., typhoid, childhood menigitis, and pneumonia) caused by antibiotic resistant bacteria.

In short, all of the evidence leads to the conclusion that enteric microorganisms associated with food animals and man, their R-plasmids, and human pathogens form a linked ecosystem in which action at any one point can affect every other. If it is the case, as the theory suggests, that the vulnerability of microorganisms to antibiotics is reduced by the use of antibiotics for nonmedical purposes in animals, the efficacy of medical treatment will be diminished in man. Potential risks to animal health also exist. And while the linkage to human health is indirect, animal agriculture faces the risk directly. The development of resistant strains, which is enhanced by subtherapeutic drug use, reduces the efficacy of those same drugs for the treatment of animal diseases.

Let me describe now the steps that led to where we are today in regulating antibiotics in animal feed.

BACKGROUND

The practice of using antibiotics in animal feeds to improve feed efficiency and the rate of weight gain became widespread in the early 1950's. It has increased steadily since that time, particularly in the feeding of beef cattle, poultry, and swine, and has been used for disease prevention in addition to feed efficiency and weight gain.

Soon after low-level feeding of antibiotics was started, FDA scientists, other scientists in the United States and scientists in other countries began studying its effects.

In April 1970, the Commissioner of Food and Drugs established a Task Force on the Use of Antibiotics in Animal Feeds. He directed the Task Force to undertake a comprehensive review of the use of antibiotics in animal feeds. The group was established on the recommendation of FDA's Science Advisory Committee, after the committee had reviewed a 1969 report issued by the British government on the use of antibiotics in veterinary medicine and animal husbandry. The British study, known as the Swann Committee Report, recommended that antibiotics be divided into "feed" antibiotics and "therapeutic" antibiotics, and that only those antibiotics not used for treatment of diseases in man be allowed in animal feeds at low levels.

FDA's Task Force report, issued in January 1972, presented conclusions generally consistent with the concerns that I have enumerated. On April 20, 1973, FDA published a regulation which required that antibiotic drugs for subtherapeutic use in animal feed meet FDA's criteria for safety based on guidelines contained in the FDA Task Force report. The regulation provided for revocation of approvals of marketed products if drug sponsors failed to provide evidence which resolved the safety issues conclusively.

The industry made commitments for, and subsequently provided the results of, a number of studies in response to the regulation. The Bureau of Veterinary Medicine reviewed the data in detail and determined that they did not meet the safety criteria. The Commissioner of Food and Drugs also asked the Agency's National Advisory Food and Drug Committee to review the data and issues involved, and to make recommendations. The Committee in turn appointed the Antibiotics in Animal Feeds Subcommittee and four expert consultants to study the issues. The Subcommittee held four public meetings, during which the drug industry, animal scientists, the Bureau, and other interested parties made presentations and comments.

After considerations of the Subcommittee and Committee recommendations, Commissioner Donald Kennedy determined, on April 15, 1977, that the Bureau should proceed with proposals to ban subtherapeutic use of penicillin in animal feeds, and to restrict the use of tetracyclines.

The Director of the Bureau of Veterinary Medicine started the statutory procedure for revoking present approvals on August 30, 1977, when he published in the Federal Register a detailed proposal to ban penicillin from animal feeds, and provided a notice to manufacturers of an opportunity for a hearing before the Agency. The Bureau published its proposal to restrict the use of tetracyclines, and its corresponding Notice of Opportunity for Hearing, on October 21, 1977. Low-level use of tetracyclines was to be eliminated except where no substitutes were available. FDA received numerous requests for hearing on the two proposals.

On January 20, 1978, we published a third proposal, which would have limited the distribution of penicillin and tetracycline premixes to feed manufacturers holding applications approved by FDA, and to farmers only on the order of a licensed veterinarian. During March and April 1978, FDA held three informal public hearings on the third proposal in agricultural areas of the United States. Subsequently, FDA decided to postpone action on the proposed distribution controls pending the results of the first two proposals.

In September 1978, the Congress allocated $250,000 for a study of the entire antibiotics in animal feeds issue, to be conducted by the National Academy of Sciences. The Congress also directed that the FDA delay implementation of its proposed restrictions pending the completion of the study.

Two months later, FDA announced, in response to the requests for hearing from drug sponsors, that it would hold a formal evidentiary hearing on its proposals to ban penicillin and to restrict the use of the tetracyclines in animal feeds. However, the start of the hearing was delayed until the release of the NAS report, which was due in March 1980.

In addition to the NAS report, other Congressionally mandated studies included the Office of Technology Assessment (OTA) report on "Drugs in Livestock Feed," published in June 1979, and the USDA's report on the "Economic Effects of a Prohibition on the Use of Selected Animal Drugs," released in December 1978. These reports essentially supported the views held by FDA. For example, the OTA report concluded that the health risks from the use of low-level antibiotics are of greater concern than the risks of cancer from DES and furazolidone as used in livestock practice. They also concluded that the drugs FDA proposed ristricting could be replaced with alternative drugs.

The USDA study which focused primarily on the potential consequences of an animal drug ban on the food and agricultural economy, concluded that, while farm and food prices would increase initially, the economic system would generally "be quite resilient to a more restrictive policy on animal drug use." This conclusion was reached even though the USDA study was based on the erroneous assumption that all feed additive antibiotics would be banned.

In the Appropriation Bill for FY 1980, the House Appropriations Committee earmarked $1.5 million of FDA's budget for a definitive epidemiological study on the antibiotics in animal feeds issue. FDA awaited the NAS report in order to consider the report's conclusions and recommendations in determining what research may be needed.

On March 18, 1980, the NAS released its report, "The Effect on Human Health of Subtherapeutic Use of Antimicrobials in Animal Feeds," prepared by its Committee to Study the Human Health Effects of Subtherapeutic Antibiotic Use in Animal Feeds. The Committee concluded that existing data neither prove nor disprove the postulated hazards to human health from subtherapeutic antimicrobial use in animal feeds. The report also stated that the lack of data linking human illness with the subtherapeutic use of antimicrobials must not be equated with proof that hazards do not exist.

The Committee stated that the research necessary to establish and measure a definite risk has not been conducted. However, in the Committee's opinion it is not possible to conduct a single, comprehensive epidemiological study of the effects on human health resulting solely from the subtherapeutic use of antimicrobials in animal feeds. The NAS committee suggested several more circumscribed and definitive studies to fill gaps in our present knowledge. However, they noted that while these studies would provide useful background information, knowledge gaps would remain. These gaps would be subject to differing scientific interpretation by those lined up on both sides of the issue.

FDA is now critically assessing the research needs in light of the NAS study. Further, we must soon decide whether to proceed with the formal evidentiary hearing on the proposed restrictions on subtherapeutic use of penicillin and the tetracyclines.

COMMENTS ON THE BILL

I will now discuss the bill, and its relation to the present procedures for restricting these drugs. The Agency has in the past and continues to have sufficient authority to take action against products such as these that pose a hazard to human health. Over the past several years we have been proceeding to implement this authority. We believe, however, that the bill's proposed statutory mechanism for limiting the subtherapeutic animal feed uses of antibiotics will assist FDA in removing these products from the marketplace. At present, FDA must hold a lengthy and resource-intensive formal evidentiary hearing mandated by section 512 of the Federal Food, Drug, and Cosmetic Act before it may take action against these uses.

At the same time, we suggest certain changes that will provide needed clarification, increase the prospects that the actions authorized by the amendment will withstand challenge in court, and improve the effectiveness of the restrictions reducing or eliminating subtherapeutic uses of certain antibiotics.

The bill should provide an explicit standard for our determination that subtherapeutic animal feed uses of a certain drug are to be restricted. Otherwise we may experience difficulty in defending our actions on judicial review. The bill now states that the Secretary may restrict subtherapeutic uses "to provide reasonable assurance of the continued effectiveness in humans of antibiotic drugs." This important goal should be accompanied by one or more criteria for us to apply. We suggest that an appropriate standard for restricting the subtherapeutic use of antibiotic drugs would be that "continued unrestricted use poses a risk of potential compromise of human therapy."

Subtherapeutic use of antibiotics in animal feed should be permitted where there is a compelling need, as provided in the bill. We suggest, however, the inclusion of a definition of the circumstances under which a compelling need could be found. We believe that the exception for compelling need should be limited to instances in which there are no approved substitutes for the prevention or control of diseases that present risks to animals or humans. The "compelling need" exception could be administered more efficiently if we were given explicit authority to determine such need on its own initiative, in addition to being authorized to act upon application.

The procedure to be followed in promulgating regulations under the proposed amendment should be clarified. We believe that explicit provision should be made for informal rulemaking under the Administrative Procedure Act, 5 U.S.C. 553. This would provide opportunity for comment by all affected, and would require preparation of a record that would be available for judicial review.

We assume that the promulgation of the regulation listing drugs that could no longer be used subtherapeutically would automatically revoke existing approvals for such uses under section 512 without the need to complete the formal proceedings begun under that section. Otherwise, the bill would offer nothing over current law. However, we suggest strongly that this point be clarified to forestall litigation of the issue.

Mr. Chairman, that completes my formal statement. I will be happy to answer any questions you or other Subcommittee members might have.

The following documents are to be submitted for the record:

1. **Proposed Rule and Notice of Opportunity for Hearing on Use of Penicillin in Animal Feed, Federal Register August 30, 1977 (42 FR 43770, 43772).***
2. **Proposed Rule and Notice of Opportunity for Hearing on Tetracycline in Animal Feeds and Tetracycline Containing Premixes, Federal Register, October 21, 1977 (42 FR 56254, 56264).***
3. **Proposed Rule on Animal Feeds Containing Penicillin and Tetracycline, Federal Register, January 20, 1978 (43 FR 3032).***
4. **Speech presented by Dr. Lester M. Crawford, Director, Bureau of Veterinary Medicine before the Committee to Study the Human Health Effects of Subtherapeutic Antibiotics Use in Animal Feed, NAS August 22, 1979.**
5. **NAS Report - The Effects on Human Health of Subtherapeutic Use of Antimicrobials in Animal Feeds.***

*** These materials may be found in the subcommittee files.**

SPEECH TO BE PRESENTED BY DR. LESTER M. CRAWFORD, DIRECTOR, BUREAU OF VETERINARY MEDICINE BEFORE THE COMMITTEE TO STUDY THE HUMAN HEALTH EFFECTS OF SUBTHERAPEUTIC ANTIBIOTIC USE IN ANIMAL FEED, NAS ON AUGUST 22, 1979

The use of antibiotics to improve growth promotion and feed efficiency in animals originated in 1949 with commercialization begun in 1950. Since that time, some 15 antibiotics and other antibacterials, either used alone or in various combinations, have been approved by FDA for use in animal feeds as well as for the clinical treatment of animals.

Antibiotics have been and still are used extensively at subtherapeutic levels in feeds for poultry, swine, beef cattle, sheep, and dairy calves.

Since the observation around 1955 that bacteria could develop a resistance to antibiotics, three hypotheses have developed, based on the contemporary standards of the day, which proposed how the feeding of antibiotics to animals could be a health hazard to humans and other animals.

First, it is known that certain pathogenic organisms such as salmonella, existing in the gastrointestinal tract of animals, can become resistant to the antibiotic(s) fed to the host animal at subtherapeutic levels and over time be passed into the environment and/or food to humans. Since the organisms are antibiotic resistant, the hypothesis is that should they produce infection in humans or other animals then the same antibiotic would be an ineffective means of treatment.

A second hypothesis concerns the ability of organisms to transfer antibiotic resistance to other organisms and therefore cause infection among people and animals that cannot be successfully treated with the same antibiotic.

A third hypothesis is that trace amounts of antibiotic residue in animal tissue, milk, and eggs may lead to the emergence of resistant strains of organisms in people.

In 1968, Great Britain, after considering earlier studies on the issue in 1960 and 62, appointed a Joint Committee on the use of Antibiotics in Animal Husbandry and Veterinary Medicine which issued the so-called Swann Committee Report in September 1969. Around this same period the Committee on the veterinary medical and the non-medical uses of antibiotics met in 1966 and the FDA Task Force on the Use of Antibiotics in Animal Feeds convened in May 1970.

Specifically, the Swann Committee was convened to investigate the connection between the subtherapeutic use of antibiotics in animal feed and the outbreak of an epidemic of Salmonella typhimurium type 29 (food poisoning) in dairy calves that subsequently spread to humans. The Committee ultimately recommended that antibiotics and other antibacterials be classed into a "feed" class and a "therapeutic" class. Antibiotics such as tetracycline, penicillin, tylosin and the antibacterials sulfonamides and the nitrofurans were to be restricted to therapeutic use only and controlled by issuance of a veterinary prescription. Antibiotics such as bacitracin, flavomycin, virginiamycin and nitrovin were to be used exclusively as "feed" antibiotics subject to directions for use.

The British Government accepted the Swann Committee recommendations in 1971. Presently, the agricultural adjustments necessitated by these restrictions have been accomplished with little disruption to the livestock economy of Great Britain. There is practically no interest in the United Kingdom in rescinding the Swann restrictions. Because of insufficient baseline data, it is difficult to quantify the benefits of the British program.

The FDA Task Force, starting with a review of the Swann Committee report issued its own report in January 1972. This report recognized the potential health hazard of drug resistant bacteria and means of transmission to humans along with the larger issue of compromising the use of drugs for therapeutic purposes. The FDA Task Force recommended the following:

A. Research

1. Define the etiology and pathogenesis of animal diseases such as shipping fever, stress, and liver abscesses wherein antibiotics are used but their role is unclear.

2. Define the safety for man and the intended species of the use of antimicrobials, that is, the morbidity and mortality; epidemiology including microbiology of isolates and the transmission of

bacteria from animals to animals and to man; drugs that will eliminate R-factors; residues including degradation products of antimicrobials which produce allergy; and the ecology of the bacterial flora of animals and the duration of shedding of certain species of bacteria.

3. Define the efficacy of antimicrobials for growth promotion and production improvements, therapy, and prophylaxis taking into consideration mechanisms of action, alternate patterns of use, dose responses, and efficacy requirements.

4. Define the methods of managing animal diseases and promoting growth with agents other than antimicrobials including the use of non-biological non-antibiotic agents, vaccines, husbandry and genetics, environment, and nutrition.

B. Restrictions on Use

The Task Force recommended the following restrictions on antibacterial agents used in feed:

1. Antimicrobial agents used in human clinical medicine that fail to meet guidelines established by the Task Force in regard to safety and/or efficacy be prohibited from growth promotion and any subtherapeutic use in animals by the following dates:

a. Tetracyclines, streptomycin, dihydrostreptomycin, sulfonamides and penicillins.

(1) In poultry - January 1, 1973

(2) In swine, cattle, and sheep - July 1, 1973

b. All other approved antibiotics - December 31, 1973.

2. The drug industry should begin immediately to develop other agents that can be used in feed to increase rate of growth and feed efficiency that do meet the criteria established by the Task Force for safety and efficacy.

3. After the dates specified in No. 1. under B on Restrictions on Use, the use in food producing animals of the following antibacterial agents - tetracyclines, streptomycin, dihydrostreptomycin, neomycin, spectinomycin, penicillins, and the sulfonamides be reserved for therapy unless they meet the criteria established by the Task Force in regard to the safety and efficacy for growth promotion or any subtherapeutic use. These antibiotics should be used only by a veterinarian or on a veterinarian's prescription, and at therapeutic levels and only for short-term treatments.

4. That antibiotics which select for bacteria resistant to the

antibiotics most critically needed for therapy of man and animals be prohibited from use in animals feeds. In this category at the present time are:

Chloramphenicol
Semi-synthetic penicillins
Gentamicin
Kanamycin

Those antibiotics which have proved to be effective and essential for the therapy of certain animal diseases and which select for R-factor mediated multiple resistance, should be available for short term use at therapeutic levels only, by a veterinarian or on his prescription.

5. That labeling for medicated feeds be required to state the amount of antibiotic in the final feed for all levels including growth levels. Revoke present regulations permitting levels up to 50 grams/ton to be quantitatively undeclared.

In 1973, the FDA published a statement of policy and criteria for testing antibiotics in order to answer the questions raised by the '72 Task Force report. Special attention was given to the tetracyclines (oxytetracycline and chlortetracycline), streptomycin, dihydrostreptomycin, penicillin, and sulfonamides as to their effect on the salmonella reservoir in animals. Manufacturers were given until April 19, 1975 to provide data on safety and effectiveness of products. Products that indicated a human health hazard would be withdrawn immediately.

During the '73-'75 era very little data was submitted by the industry to answer the questions raised above and that which was submitted was for the most part declared to be inadequate.

In 1976, the Antibiotics in Animal Feeds Subcommittee, which was a part of the National Advisory Food and Drug Committee, met on four (4) occasions to consider the future of penicillin, the tetracyclines (chlortetracycline & oxytetracycline), and sulfaquinoxaline used at subtherapeutic levels in the feed of food-producing animals. Recommendations were presented in January '77 and stated the following:

Penicillin

1. Discontinue use in all species for purposes of growth promotion and/or feed efficiency.

2. Discontinue use of disease prevention as approved for chickens, turkeys and rabbits. This use is to be limited, to the extent possible, to those periods of time for which the presence of the drug in the feed is necessary due to the threat of animal disease.

Tetracyclines

1. Discontinue use of growth promotion and/or feed efficiency in all species for which effective substitutes are available.

2. Continue use for disease prevention where effective alternates are not available and as approved for the various species. This use is to be limited, to the extent possible, to those periods of time for which the presence of the drug in the feed of a particular animal species is necessary due to the threat of animal disease.

The Subcommittee also advised several GENERAL RECOMMENDATIONS:

1. The establishment of regulatory measures to assure that the antibacterial drugs in animal feeds are used in a judicious manner, by limiting sale of products containing the tetracyclines and penicillin to feed mills and/or producers who are the holders of an approved (FD-1800) Medicated Feed Application. However, the Subcommittee recognized that such action removes the product from use by a practicing veterinarian if he is not the owner of a registered feed mill. With this in mind, the Subcommittee further recommended that an order from a licensed veterinarian be recognized as a second means of distribution of these products and that each of these procedures be carefully monitored to assure compliance.

2. To monitor, perhaps in cooperation with NCDC, the development and transfer of antimicrobial resistance in those organisms capable of inducing disease in man and animals, and to establish a baseline on current antibiotic resistance for use in future evaluations.

3. Continue to evaluate the effects of implementation of national recommendations in other countries.

4. **Re-evaluate the effect of the subtherapeutic uses of antimicrobial products in animal feeds in this country within 5 years.**

5. **Affirm that the long-term goal of the FDA is the elimination to the extent possible, from low level animal feed use, of those drugs also used for therapy of disease in man. This should be accomplished as satisfactory alternative measures for disease prevention in animals become available; e.g., substitute drugs, vaccines, new husbandry practices, genetic improvements, etc.**

6. **Promote research regarding the mechanism of growth promotion and disease prevention in food producing animals.**

7. **Foster the creation of a highly scientific and specialized committee to attempt to establish the magnitude and to define the future significance of the human health risk that has evolved from the increasing bacterial resistance to antibiotics in man and animals.**

The NAFDC accepted the recommendations on penicillin and sulfaquinoxaline but refused to support the views on the tetracyclines and recommended that no changes be made at that time. The NAFDC further endorsed the seven General Recommendations made by the Subcommittee. However, the Subcommittee recognized that a practicing veterinarian would not be able to use the products if the recommendations were accepted so it recommended that an order from a licensed veterinarian be recognized as a second means of distribution of these products and that each of these procedures be carefully monitored to assure compliance.

On April 15, 1977 the FDA Commissioner, Donald Kennedy responded to the NAFDC recommendations. FDA concurred with the recommendations on penicillin and sulfaquinoxaline but rejected the recommendation to continue the marketing of the tetracyclines. Instead, Commissioner Kennedy indicated he would proceed to restrict the drug's labeling to growth promotion in certain minor animal species and disease control claims for which effective substitutes are not available, thereby discontinuing all non-essential uses. Further, he proposed to impose further restrictions in the marketing of these drugs by proposing that penicillin and the tetracyclines (OTC & CTC) only be used in animal feed following the written order of a licensed veterinarian.

Dr. Kennedy gave his reasons why the FDA would take the above steps. He indicated that FDA recognized the benefit of the use of these drugs in certain animal diseases. Further, he recognized that at least in some significant diseases, adequate substitutes, either other antibiotics or other methods of control, were not currently available for these diseases. By limiting claims to those drugs for which there were no substitutes, and by placing these drugs under regulations that require a veterinarian's order, FDA's intention was to: (1) insure, to the extent possible, that the drug will be placed in the hands of individuals who, by training and background, are suited to administer drug products; (2) assist in seeing that the most appropriate antibiotic is used at the most effective level for the shortest time necessary to achieve the desired result(s); and (3) insure that a valuable management tool (i.e. the tetracyclines) continue to be available to the animal industry, when needed.

Next, Dr. Kennedy presented the scientific rationale for taking such actions.

(1) Information indicated that human E. coli and those of other mammals are not separate and distinct strains, but interchangeable between man and other species; (2) The R-plasmids themselves are likely not distinguishable into "human" and "animal" types; (3) Evidence suggested that individuals having close contact with animals or with uncooked meat have significantly elevated populations of resistant enteric bacteria; and (4) R-plasmids could be exchanged in humans between enteric bacteria and some non-enteric pathogens.

Continued unrestricted use of the tetracyclines would result in selective pressure that would continue to increase the pool of drug-resistant bacteria in the ecosystem. Although FDA could identify no specific instance in which human disease was more difficult to treat because drug resistance has arisen from an animal source, it was probable such problems had gone unnoticed. The theoretical possibility that drug-resistant pathogens produced by antibiotic selection had become a real threat with the emergence of human diseases (typhoid and childhood meningitis) caused by ampicillin-and chloramphenicol-resistant Salmonella and Haemophilus. The point is that known routes of transfer exist by which antibiotic use in animals can contribute to such threats.

The evidence indicated enteric microorganisms in food animals and man, their R-plasmids, and human pathogens formed a linked ecosystem. Viewed in this light, the vulnerability of microorganisms to antibiotics was a kind of "pool". The experts on infectious disease and public health on the Task Force, the Subcommittee, and others whom Dr. Kennedy consulted in connection with this action, were decidedly of this view.

FDA formally published its proposal to ban penicillin from animal feeds in the FEDERAL REGISTER, August 30, 1977. The proposal to restrict the use of tetracyclines was published October 21, 1977. Drug manufacturers have asked FDA to hold formal evidentiary hearings on both proposals.

On January 20, 1978, FDA published a third proposal concerning antibiotics in animal feeds. This proposal would limit the distribution of feeds containing penicillin or tetracyclines to feed manufacturers holding applications approved by the FDA and on the order of a licensed veterinarian.

There have been several developments since the proposals were published.

*During March and April, 1978, FDA held public hearings on the proposed distribution controls in Ames, IA, Raleigh, NC, and Dallas, TX. At these hearings, livestock and poultry producers and other interested parties expressed concern about the practicality of the controls. For example, there was concern that there may not be enough veterinarians in some areas to write orders for the feed, as the proposal would require. Others questioned whether state pharmacy laws would pose difficulties in implementing the requirement for a veterinarian's order.

*In August, 1978, FDA postponed action on the proposed distribution controls until the issues raised at the public hearings were resolved.

*In September, 1978, Congress made this postponement mandatory when it earmarked $250,000 for additional research on the use of antibiotics in animal feeds. This research was to be planned and monitored by the National Academy of Sciences.

*In November, 1978, FDA announced that it would hold an administrative (formal evidentiary) hearing on its first two proposals, i.e., the penicillin and tetracycline restrictions. The hearing had been requested by the manufacturers of the antibiotics. It will be held before an administrative law judge who, based on the evidence, will recommend to the FDA Commissioner what final action to take.

Also, in November '78, the FDA began contract negotiations with the National Academy of Sciences in an effort to meet the Congressional mandate. The final contract was cut on March 23, 1979.

While the NAS contract was being negotiated the FDA's Bureau of Veterinary Medicine continued its review of the issue and proceeded to articulate the issues based on available data. The Bureau saw that it had three options- (1) vacate the entire issue and go into a research monitoring phase; (2)

to indefinitely postpone action; (3) to proceed toward withdrawal. After some deliberation, the Bureau concluded the proper course was to proceed toward withdrawal by holding the evidentiary hearings in the Spring of 1980.

Recent trips to Great Britain and to the World Veterinary Congress in Moscow by the Bureau's top management also affected the above decision. While there, I assessed the British situation and conferred with a number of American and foreign experts in the field. Also, the recent release of the OTA Report on "Drugs in Livestock Feed," which essentially agrees with FDA's original intent to withdraw the antibiotics from feed, has contributed to the decision to proceed.

Great Britain, as you know, for a decade has been operating under an antibiotic restriction program similar to that which BVM proposed in 1977. Personal inquiries lead BVM to concur with Peter Best, (Feed Management; July '79)" ... there is no evidence that the production results from Britain's farms have been seriously affected by the imposition of tougher drug controls. The comment one hears from both veterinarians and feed manufacturers is that this has been due to an overall improvement in livestock health and husbandry. Where low level antibiotics previously covered up bad management, it is said, such practices are now exposed and rectified. There are also some convincing data available on the cost-effectiveness of using the feed antibiotics, even though the price of some of them can work out at around $5 per ton in the finished feed. So in Britain today it is rare to hear strong objections being raised to the restrictions imposed by the post-Swann laws".

The OTA report speaks directly and succinctly to the matter at hand. Their conclusions appear, eminently valid:

1. Drugs in animal feed are targeted for multiple purposes--40 percent of all antibacterials produced are used for animal feed.

2. Because of the attendant risks, regulatory attention has focused on the addition of low levels of antibacterials in animal feeds and on DES, a proven human carcinogen.

3. The health risks from the development of bacterial resistance to antibacterials in feed are of greater concern than the risks of cancer from DES and furazolidone as used in livestock practices.

4. Most of these drugs could be replaced with alternative drugs that are already approved by FDA.

5. The economic consequences of removing these drugs could be significant over the short term. Production may be decreased in the period immediately following a ban, but higher prices may offset the decrease in quantity and may lead to higher producer incomes. But consumer prices would also be higher.

6. The tradeoff is therefore between immediate economic benefits and future

health risks. These decisions involve value judgments that cannot be based simply on monetary considerations. And the lack of scientific certainty on the magnitude of both the probable health risks and the attributed increases in meat production makes the formulation of a balance-sheet approach difficult.

OTA's recommended Option 1 (Allow FDA to Decide the Issues, Subject to Congressional Oversight) is the proper way to proceed. FDA has announced evidentiary hearings will be held and thus the issues will be subjected to an impartial, public forum.

The Bureau's internal review of comments from industry, the results of public hearings and a review of the literature have led us to the following conclusions on penicillin:

Drug resistant _E. coli_ of animal origin are a) indistinguishable from _E coli_ of man; b) are transmitted to man; c) colonize man; d) transfer their plasmids to normal human flora and pathogens.

Drug-resistant pathogens derived from animals pose a potential human health hazard which can be life threatening in certain individuals.

Therapeutic effectiveness studies have not been conducted which would change the NAS/NRC rating of "probably not effective" for the feed uses of penicillin.

Adequate data are unavailable to demonstrate the effective levels of penicillin for growth promotion.

Bacteria harboring R-plasmids are not less virulent than other bacteria; furthermore, antibiotics may select for plasmids with resistance genes linked to pathogenicity factors.

As regards the tetracyclines, we have assessed the scientific evidence and concluded:

R-plasmids develop in domestic animals which are fed subtherapeutic amounts of the tetracyclines.

Low levels of the tetracyclines lead to selection of drug resistant E. coli which are a) indistinguishable from E. coli of man; b) are transmissable to man; c) colonize man; d) transfer their plasmids to normal human flora and pathogens.

Use of subtherapeutic tetracyclines has been shown to result in the shedding of resistant Salmonella.

Salmonella and other pathogens causing disease can be transmitted from animals to man. These pathogens, when drug resistant, can be refractory to antimicrobial thereapy.

Bacteria harboring R-plasmids are not less virulent than other bacteria;

furthermore, antibiotics may select for plasmids with resistance genes linked to pathogenicity factors.

As we have publicly stated recently, one cannot but be disturbed at the reaction that has surrounded BVM's low level antibiotic proposals. Historically, however, most such proposals have met with swirling controversy--water purification, pasteurization of milk; rabies vaccination; brucellosis eradication; bovine tuberculosis eradication; etc. In none of these issues were KOCH's postulates satisfied--there was no human experimentation and there were no bodies in the streets. But the incidence of typhoid fever, rheumatic fever, scarlet fever, human rabies, undulant fever, spinal tuberculosis, and other human maladies were materially reduced by the controversial measures mentioned above.

Although there is an appearance of disagreement within the scientific community, no one would disagree that continuous sub-therapeutic feeding of penicillin or tetracycline encourages the development of bacterial resistance. No responsible person would disagree that diseases caused by resistant organisms are difficult to cure. Thus, what appears to be controversy is for the most part the contrivance of special interest groups.

BVM receives virtually no input questioning the scientific rationale of the proposed restrictions. What we are getting with increasing frequency are letters asking why we are not taking steps to preserve the efficacy of veterinary antibiotics.

Dean W.R. Pritchard of the University of California School of Veterinary Medicine recently wrote, "we recognize the risk to human (and animal) health created by this practice and believe that some control is needed." Professor Lloyd Davis of the University of Illinois College of Veterinary Medicine stated in an August 6th letter, "Increasingly, we are seeing individual patients and herds with infections caused by multiply-resistant strains of pathogens. Some of these isolate are not susceptible to any antibiotic which would be economically feasible to employ in therapy." Professor John M. Bowen of the University of Georgia recently stated that there was no question low-level feeding produced resistant organisms which could cause disease in man.

Dr. Richard P. Novick of New York's Public Health Research Institute has stated, "Thus, during the past 25 years we have witnessed the dramatic yet highly predictable development of large and spreading populations of multi-resistant bacteria that reach the human population from livestock in large numbers. They also exchange plasmids and other genetic elements with considerable frequency, and are involved in qualitatively new types of genetic events in which genes involved directly in the causation of disease are joined to those that determine antibiotic resistance."

I wrote (Proceedings, Fourth Annual Conference for Veterinarians, University of Georgia) in 1967 that "the time has come to remove essential antibiotics from the feed bag." Since that time the numbers of E. coli isolates resistant to tetracycline has increased to over 90%. A semi-synthetic penicillin, ampicillin, which was nearly 100% effective against coliforms in 1967 now is

only 22% effective against E. coli and only 25% effective against Salmonella typhimurium.

The obvious gambit of the regulated industry is to ask for more studies.--a maneuver which has forestalled the proposed reforms for over a decade. The so-called controversy is reminiscent of the Bastian-Pasteur debates of the last century. Bastian, and many others, were never able to accept the germ theory and continued to ask for more studies.

Regulation by delay is simply not good stewardship of the public trust. The time to decide these issues is now and the medium for that decision is the evidentiary hearings which we intend to hold next Spring.

Mr. WAXMAN. Ms. Foreman.

STATEMENT OF CAROL TUCKER FOREMAN

Ms. FOREMAN. Yes, Mr. Chairman, I appreciate the opportunity to discuss with the subcommittee the agricultural practice of adding antibiotics to feed to prevent illness and promote growth in farm animals. [See p. 460.]

The U.S. Department of Agriculture shares the growing concern that widespread farm use of antibiotics may foster the development of disease-causing organisms that are resistant to many antibiotics.

There is concern that resistant bacteria will then be transferred to humans and that the antibiotics now used to treat many human illnesses will not be effective against these bacteria. The Department is, therefore, in sympathy with the primary concern of H.R. 7285.

The USDA's Food Safety and Quality Service monitors the Nation's meat and poultry supply for the presence of chemical residues, including animal drugs, that may be harmful to human health.

Before a drug may be used in animal feed or administered directly to food animals, it must first be approved by the Food and Drug Administration. FDA also sets a tolerance level for each drug. Meat or poultry products containing residues of these drugs above the tolerance level are legally adulterated.

USDA is responsible for enforcing the tolerance levels.

The use of agricultural chemicals and the development of sophisticated methods of detecting their residues in meat and poultry have grown enormously over the past 30 years.

The discovery in World War II that pesticides such as DDT could be used to destroy certain insect pests and plants kindled the interest of agriculturalists in attacking other pest and disease problems with chemicals and resulted in the enormous growth of their use in animal production.

Over the same period of time we have seen the development of new analytical techniques capable of detecting low levels of chemical residues in food.

Because of the new analytical techniques, the full consequences of the use of drugs in animal production are beginning to be known. Scientists are finding that dangerous chemicals have become ubiquitous in the environment, the air we breathe, the water we drink, and the food we eat. They result not only from agricultural uses but also from the widespread industrial use of new chemicals and have caused rising public concern.

The Government has taken a number of actions to respond to the rising public concern. One of them was the creation of the Department of Agriculture's national residue program in 1967. It is the first attempt to test consistently and regularly for chemical residues in meat and poultry products. Today the program has a budget of $4.5 million but it still does not provide the coverage it should to protect the American people adequately from potentially dangerous chemicals.

We will have in addition serious technological barriers. Although our residue program tests for 45 chemicals that are used in agricultural production, there are at least 100 other toxic chemicals that may be present in food and for which there are no reliable methods of detection.

Those that are available are very expensive and it isn't realistic for us to test every carcass for all residues.

For this reason, we do our residue sampling on a statistical sampling basis that provides a 95 percent assurance that if a violation rate of 1 percent or more exists in the national animal population, it will be detected in the course of a year. However, the plan leaves open the possibility that a significant but localized contamination incident will go undetected.

Antibiotic residues are an object of special concern for us. About half the antibiotics used in this country are employed in agriculture, and of these, 80 percent are used as feed additives in subtherapeutic management. There are 20 or so antibiotics in common use; of these we test for about half, including the penicillins and tetracyclines.

While nearly all of the commonly used antibiotics can be detected, only those most frequently used can be precisely identified. Those that cannot be identified are lumped together in the general category known as unidentifiable microbial inhibitors.

In order to better deal with this situation, our scientists developed a much faster test for antibiotic residues, called STOP—for swab test on premises. This test enabled us to determine whether or not an animal was in violation within 24 hours, rather than 7 to 14 days.

We are now beginning to turn more of our attention to areas where subtherapeutic misuse has led to problems. Violative residues occur in almost all food animals, and residues below violative levels—which are legal at present tolerances—occur in even greater percentages. A violative level is one that exceeds the tolerance point established for a particular drug. For penicillin, the tolerance is 0.05 parts per million; for tetracycline it is 0.25 parts per million. If meat contains residues greater than these amounts, it is considered adulterated and should not be permitted in human food channels.

It is significant that we register only those levels of antibiotics that we can presently detect. It is safe to say that the near future will bring technical advances that will reveal even wider dissemination of low-level antibiotic residues and it may be necessary at that time to consider lowering the legal tolerances.

Even at present tolerance levels we are encountering several problems that result from the use of antibiotics. I have already mentioned the high rate of violations in dairy cows. We are now attempting to deal with the problem of violative antibiotic residues in calves.

In 1979 the residue monitoring program analyzed 1,485 samples from calves for antibictic residues and 91 were violative. Two years ago the monitoring program began to pick up a significant problem with antibiotics, primarily tetracycline in swine.

These figures are worrisome because careful subtherapeutic use of antibiotics should not result in violative levels. The number of violations we are finding indicate that the subtherapeutic use of antibiotics is often not confined to low levels of the drug.

It is often difficult to draw a distinct line between therapeutic and subtherapeutic use. With young calves, for example, it appears that many owners are administering high levels, not to cure illness—therapeutic use—but to prevent illness during stressful periods such as moving or auction. At these high levels violations are likely unless the animals are properly withdrawn from the drugs.

In the near future we will be extending the STOP program to calves. The violations in swine may be the result of the intense effort over the past 2 years to deal with the problem of sulfa drugs in this species.

Our effort to reduce sulfa violations in swine has been successful, but perhaps because of the highly visible effort to solve this problem some producers have been substituting antibiotics for sulfa.

In conclusion, we must admire and appreciate the enormous production of American agriculture and the role which antibiotics have played in supporting that production.

We must wonder, however, at the potential ultimate cost. In the heady days of economic and technological expansion following World War II, the notion of adverse, unintended consequences resulting from extensive use of chemicals did not enter the public consciousness. Today, out of necessity and experience, we are more self-conscious of our actions and their consequences.

I should emphasize that we are just beginning to understand the effects of rapid technological change upon the food system and upon public health. The potential transfer to humans of resistant bacteria must therefore receive our most careful attention.

Thank you.

[Testimony resumes on p. 512.]

[Ms. Foreman's prepared statement follows:]

STATEMENT BY CAROL TUCKER FOREMAN
ASSISTANT SECRETARY FOR FOOD AND CONSUMER SERVICES
UNITED STATES DEPARTMENT OF AGRICULTURE

Mr. Chairman, I appreciate this opportunity to discuss with the subcommittee the agricultural practice of adding antibiotics to feed to prevent illness and promote growth in farm animals. The U.S. Department of Agriculture shares the growing concern that widespread farm use of antibiotics may foster the development of disease causing organisms that are resistant to many antibiotics. There is concern that resistant bacteria will then be transferred to humans and that the antibiotics now used to treat many human illnesses will not be effective against these bacteria. The Department is therefore in sympathy with the primary concern of H.R. 7285 that the increase in the number of antibacterial organisms poses a potential health hazard to humans and animals.

The USDA's Food Safety and Quality Service monitors the nation's meat and poultry supply for the presence of chemical residues, including animal drugs, that may be harmful to human health. Before a drug may be used in animal feed or administered directly to food animals, it must first be approved by the Food and Drug Administration. FDA also sets a tolerance level for each drug. Meat or poultry products containing residues of these drugs above the tolerance level are legally adulterated. USDA is responsible for enforcing the tolerance levels. Since our enforcement is based on information gained from the residue monitoring program, I think it would be useful to briefly describe this program. I will then discuss some of the problems we have encountered in the specific area of antibiotic residues.

USDA's National Residue Program was founded in 1967 but its origins can be found in two related historical trends that occurred in the period following the Second World War. The first was the "toxics revolution" in American agriculture. The discovery following World War II that pesticides, like DDT, could be used to destroy certain insect pests of plants kindled the interest of agriculturalists in attacking other pest and disease problems with chemicals. Scientists and technologists responded to the problem with ingenuity and developed a whole host of chemical solutions to farm problems. DDT and other chlorinated hydrocarbons such as chlordane, heptachlor, dieldrin, and aldrin were introduced and used widely to combat pests. And, of great historical significance, was the contemporaneous discovery of antibiotics and the development of drugs such as penicillin and tetracycline that were originally fed or injected into animals to alleviate disease but were soon found to prevent disease and promote growth. It therefore became possible to organize production into fewer but much larger units, and to raise animals in crowded but economical spatial conditions which before would have given rise to infectious diseases. As a result of these and other factors, American agriculture became dependent on pesticides, drugs, and antibiotics to maintain high levels of production.

The second trend was the development of new analytical techniques capable of detecting low levels of chemical residues in food. In the late 1940's, the techniques for detecting residues in food were rudimentary. At the Department of Agriculture, for example, technologists would place a piece of meat in water along with a mosquito larva. If the larva died, then it was considered likely that residues of DDT or other potentially dangerous chemicals were present in the meat. In the late 1950's, sophisticated new analytical techniques, such as gas chromatography and mass spectrometry, came into use. These techniques enabled government scientists to detect chemical residues at progressively lower levels, and to determine more readily the exact chemical or chemicals present.

Because of the new analytical techniques, the full consequences of the "toxics revolution" began to be known. Scientists found that dangerous chemicals had become ubiquitous in our environment: in the air we breathe, the water we drink, and the food we eat. They resulted not only from agricultural uses, but from the widespread industrial use of new chemicals. Rising public alarm (Rachel Carson's Silent Spring was one notable example) led to a series of government actions to control toxic chemicals. The founding of USDA's National Residue Program in 1967 was one of these actions. The Department previously had tested for chemicals in meat and poultry, but not on a systematic, nationwide basis. Before 1967, for example, if an inspector had noticed a staggering steer in a slaughterhouse pen, the Department might have tested for the presence of lead on the asumption that the steer might have been poisoned by licking some paint from a fence. But there was no systematic sampling in the absence of overt signs of contamination.

While it represented an important step forward when it began years ago, the National Residue Program was at first a rather modest undertaking. During the first year, approximately 1,000 tests were run on meat and poultry samples. About 700 of the tests were for antibiotics, and the remainder were mostly for chlorinated hydrocarbons (such as DDT) and trace elements (such as mercury or lead). The budget during that period was about $100,000 per year, and there were only two people in Washington associated directly with the residue program on a full-time basis.

The residue program today has a budget of $4.5 million, and a Washington based staff of 50. In 1979, approximately 25,000 samples from meat and poultry were tested for the presence of 43 chemical residues. Despite this growth, the program still does not provide the coverage it should to protect the American people adequately from potentially dangerous chemicals. During this period, national and international contamination incidents and concerns over residue problems escalated faster than the program's rate of growth. In addition, there are still significant technological barriers. Although the program tests for 43 chemicals, there are 100 other toxic chemicals that may be present in food, and for which there are no reliable methods of detection. Those that are available are expensive. FSQS cannot realistically test every carcass for all residues. Some 120 million livestock and 3.5 billion poultry are inspected and marketed each year. The cost of testing all of them for residues would run about $100 billion a year.

For this reason, the present National Residue Program is based on a statistical sampling plan that provides a 95 percent assurance that if a violation rate of one percent or more exists in the national animal population, it will be detected over the course of a year. This plan leaves open the possibility that a significant but localized contamination incident will go undetected.

Within the present framework, FSQS is already taking steps to improve its residue program. In 1978, we published a study entitled, A Strengthened Meat and Poultry Inspection Program, which emphasized the need for changes in the inspection program to put the agency in a stronger position to deal with the mounting problems of chemical residues. A 1979 General Accounting Office report, and hearings by the Subcommittee on Oversight and Investigations, House Commerce Committee in 1978, have both emphasized the critical importance of improving the effort against residues.

The fiscal year 1980 budget provided an additional $1,477,000 to enlarge laboratory capabilities, expand the number and range of tests, increase the number of animals tested and speed up the reporting of results to animal producers. In addition, FSQS has developed and put into use a rapid test method for antibiotics that permits testing for certain residues in the slaughtering plants on the day of slaughter, and is working to develop other rapid screening tests. I will have more to say about this in a minute. Furthermore, we are considering requesting Congress to grant us the statutory authority to require identification of all animals as they come to slaughter and to quarantine animals on the farm if they are suspected of contamination.

We believe that identification and quarantine authority would be a tremendous help in dealing with residue problems. When the monitoring program detects illegal residues which indicate that a producer is not properly administering animal drugs, or that animals at a farm or feedlot have inadvertently become contaminated, we cannot fully control the problem unless we can trace the contaminated animal back to the farm or to the source of contamination. The identification of all animals at slaughter would enable us to accomplish this essential step of trace-back very quickly. Quarantine authority would enable us to move in orderly fashion to clean up residue problems at the source without disrupting the markets for noncontaminated animals. We are now considering a legislative proposal to buttress our residue program with these new statutory tools. This proposal would be in line with the recommendations made by the General Accounting Office in their 1979 report, Problems in Preventing the Marketing of Raw Meat and Poultry Containing Harmful Residues.

Viewed in historical perspective, the FSQS residue program is a relatively young and developing program. The future development of the residue program will depend upon continued public recognition of the critical nature of chemical residues in food and the imaginative application of new policy and technology.

Antibiotic residues are an object of special concern for us. About half the antibiotics used in this country are employed in agriculture, and of these, 80 percent are used as feed additives in sub-therapeutic management. There are 20 or so antibiotics in common use; of these we test for about half, including the penicillins and tetracyclines. While nearly all of the commonly used antibiotics can be detected, only those most frequently used can be precisely identified. Those that cannot be identified are lumped together in the general category known as "unidentifiable microbial inhibitors."

Until recently much of our attention has been focused on the misuse of antibiotics for therapeutic purposes. Residues resulting from injectable antibiotics are a particularly dangerous problem because of the high levels at which they often occur. One very troublesome area has been the misuse of injectable antibiotics for dairy cows. At one point, not long ago, violations were running as high as 30 percent among suspect animals. Dairy farmers use antibiotics to treat diseases such as acute mastitis, chronic mastitis, and pneumonia in cows. These diseases are common in dairy cows because they are under a great deal of stress as a result of being milked every day by machines. However, violative levels should not appear in the tissue of slaughtered dairy cows if proper withdrawal periods are observed. A cow being treated with penicillin should be withdrawn from the drug 5 days before slaughter. For tetracycline the withdrawal period is 21 days. The high violation rate indicates that many farmers may not have been observing these withdrawal periods.

In order to better deal with this situation, our scientists developed a much faster test for antibiotic residues, called STOP--for Swab Test on Premises. This test enabled us to determine whether or not an animal was in violation within 24 hours, rather than 7 to 14 days, as was the case with older analytical methods. Before instituting the program in February of 1979, we went out to the public with an extensive informational and educational campaign. The results have been very positive. At the time STOP was begun in early 1979, our surveillance program was finding that about 30 percent out of dairy cows with needle marks or other signs of antibiotics did in fact have violative residues The percentage is now down to 15 percent, and more important, far fewer cows now exhibit the overt signs of the misuse of antibiotics. We therefore have been able to expand the STOP program from a small segment of producers to include all major producers.

We are now beginning to turn more of our attention to areas where subtherapeutic misuse has led to problems. Violative residues occur in almost all food animals, and residues below violative levels--which are legal at present tolerances--occur in even greater percentages. (A violative level is one that exceeds the tolerance point established for a particular drug. For penicillin the tolerance is .05 parts per million; for tetracycline it is .25 parts per million. If meat contains residues greater than these amounts it is considered adulterated and should not be permitted in human food channels.)

It is significant that we register only those levels of antibiotics that we can presently detect. It is safe to say that the near future will bring technical advances that will reveal even wider dissemination of low-level antibiotic residues, and it may be necessary to consider lowering the legal tolerances.

Even at present tolerance levels, we are encountering several problems that result from the use of antibiotics. I have already mentioned the high rate of violations in dairy cows. We are now attempting to deal with the problem of violative antibiotic residues in calves. In 1979, the residue monitoring program analyzed 1,485 samples from calves for antibiotic residues, and 91 were violative. Two years ago, the monitoring program began to pick up a significant problem with antibiotics (primarily tetracycline) in swine. In 1978, out of 1,352 samples from swine analyzed for antibiotics, 67 contained violative residues. In 1979, 24 of 1,609 were violative. Projected to the national animal population, animals, the violation rate for antibiotics in calves is 6percent, and is 1.5 percent in swine compared to 5 percent in 1978.

These figures are worrisome because careful subtherapeutic use of antibiotics should not result in violative levels. The number of violations we are finding indicate that the subtherapeutic use of antibiotics is often not confined to low levels of the drug. It is often difficult to draw a distinct line between therapeutic and subtherapeutic use. With young calves, for example, it appears that many owners are administering high levels, not to cure illness (therapeutic use), but to prevent illness during stressful periods such as moving or auction. At these high levels, violations are likely unless the animals are properly withdrawn from the drugs. In the near future we will be extending the STOP program to calves. The violations in swine may be the result of the intense effort over the past 2 years to deal with the problem of sulfa drugs in this species. Our effort to reduce sulfa violations in swine has been successful, but perhaps because of the highly visible effort to solve this problem, some producers have been substituting antibiotics for sulfa.

In conclusion, we must admire and appreciate the enormous production of American agriculture and the role which antibiotics have played in supporting that production. We must wonder, however, at the potential, ultimate cost. In the heady days of economic and technological expansion following World War II, the notion of adverse, unintended consequences resulting from extensive use of chemicals did not enter the public consciousness. Today, out of necessity and experience, we are more self-conscious of our actions and their consequences. I should emphasize that we are just beginning to understand the effects of rapid technological change upon the food-system and upon public health. The potential transfer to humans of resistant bacteria must therefore receive our most careful attention.

Mr. Chairman, this completes my testimony. I will be happy to respond to any questions.

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Mr. WAXMAN. Thank you very much.
Mr. Hjort.

STATEMENT OF HOWARD W. HJORT

Mr. HJORT. Thank you, Mr. Chairman.

I do appreciate the opportunity to appear before this committee to present the views of the U.S. Department of Agriculture on H.R. 7285, "The Antibiotic Preservation Act."

This bill, which would restrict the subtherapeutic use of antibiotics in animal feeds, addresses a very complex issue.

It is accepted that the sustained use of an antibiotic in humans or animals results in the development of strains of certain bacteria which are resistant to the same, and in some instances other, antibiotics. Such resistance becomes a serious concern if it makes the use of these antibiotics less effective in treating human or animal disease.

But, while it would appear a logical extension, the scientific evidence linking the low-level feeding of antibiotics to the development of resistant strains of pathogenic bacteria in humans remains quite tentative. In fact, on March 18, 1980, a congressionally mandated study by the National Academy of Sciences concluded that existing data neither prove nor disprove the postulated hazards to human health from the low level use of antibiotics in animal feeds.

Animal agriculture has come to rely upon the use of several antibacterial compounds for the prevention of disease and growth enhancement. Of these antibacterials, tetracyclines are used in the greatest quantity and their use is the most widespread as feed additives for growth promotion and/or disease prevention in livestock and poultry feeds.

The Department of Agriculture is on record as supporting, in principle, rulemaking proposals that are designed to minimize dangers to human and/or animal health and safety. The Department is therefore in sympathy with the primary concern of H.R. 7285 that the increase in number of antibacterial resistant organisms poses a potential health hazard to humans and animals.

However, as we have noted, any such increase in disease-resistant organisms in humans stemming from present practices involving the subtherapeutic use of antibiotics in animal agriculture remains largely theoretical. The reasonable—though somewhat disappointing—conclusion of the National Academy of Sciences National Research Council underscores the belief that ironclad scientific data may never be available to help resolve the issue one way or the other.

In areas where there is such uncertainty and only a potential risk is recognized, we believe it is prudent to weigh the costs and benefits of any new or alternative action. If it is correct, for example, that the continued subtherapeutic use of certain antibiotics will ultimately result in making these same drugs ineffective for use in treating human and animal diseases, the costs of failing to restrict their use now could be very high indeed.

If, on the other hand, the linkage between subtherapeutic animal drug use and resistance to treatment of disease in humans proves to be inconsequential and, knowing that the benefits to animal agriculture are real, the costs to food consumers of restricting the use of these antibiotics also could be high.

The possibility of this result is made more likely if a decision to restrict usage is made without effective and economic suitable substitutes being available.

A third possibility also exists. If it can be shown that the subtherapeutic use of selected animal drugs contributes little to the continued productivity of contemporary animal agriculture, or if suitable substitutes are readily available and continue to be authorized for use, the decision becomes easier.

Under such circumstances, the potential costs of a decision to restrict usage in order to eliminate even a theoretical human health threat are reduced considerably. Thus decisionmaking on this issue is a serious and complex matter.

The current law regulating the current use of antibiotics is quite specific. It does require the Food and Drug Administration to ban the continued approval of an animal drug if it finds that "new evidence shows that drug is not safe for use."

We do not believe that the solution to this problem will be found by taking one simple regulatory action. H.R. 7285 contains a very important feature in that regard. As we understand the proposed legislative change, the Secretary of Health and Human Services would retain the administrative flexibility to make the final decision on specific drugs on a case-by-case basis—a power which he already has. And, it would require that rulemaking take place within 180 days of enactment.

You have already heard from several witnesses regarding the human health aspect of subtherapeutic animal drug use.

Before offering specific comments on the bill you are now considering, let me first discuss another aspect of this issue—the broader question of antibacterial drug use from the perspective of animal agriculture.

Farmers have used antibacterial drugs at subtherapeutic levels in feed for approximately 30 years. Over the years they have come to believe that such use reduces the risk of animal disease outbreaks and improves growth rate and feed efficiency.

The changes which have occurred in animal agriculture in the United States tend to support that belief. The widespread and routine use of antibacterials is closely identified with changes in the structure of the U.S. livestock and poultry industry. The ability to suppress and control many infectious animal diseases has often been cited as a factor facilitating the development of large-scale, confined rearing operations.

Many producers believe that the subtherapeutic use of animal drugs is essential to continued productivity in agriculture.

On the other hand, there are producers in this country who voluntarily have eliminated the use of such additives in feeds. To date, we are not aware of any major health animal problems they have had as a result of their chosen practice.

The available scientific data also tend to support the belief that subtherapeutic feeding of antibiotics is effective in controlling disease and promoting growth in animals. While most of the data are from tests conducted in the 1950's and 1960's following the introduction of these antibiotics, less numerous recent studies tend to verify their continued efficacy.

Farmers need current research data to know how cost effective this practice continues to be after 30 years; and policymakers need to know and understand the food price and farm income implications of any action taken to remove a potential risk to human health.

There are also limited data to document whether, and to what extent, the use of antibiotic drugs in animal feeds has resulted in any compromise of therapy related to disease. Again, casual observation of U.S. animal agriculture—the longest and most widespread experiment we have on the effects of drug use—indicates no evidence of an increase in animal diseases or serious interference in therapy attributable to such use.

Thus, even though risk is present, there have been no major disease outbreaks in animal agriculture that have shown the common feed additivies—penicillin and tetracycline—to be any less effective in fighting disease than in earlier times.

A final scientific concern relates to the availability, effectiveness and cost of substitute drugs. The bill you are now considering would only remove the authorization for subtherapeutic use of these drugs which are also used in humans to fight infectious diseases.

Other regulatory proposals awaiting final decision would remove approval for use at subtherapeutic and therapeutic levels of certain substitutes such as nitrofurans. Presumably, usage would not be withdrawn unless substitutes were available.

As you already know, several western European countries have taken action similar to that proposed in H.R. 7285. The results of their policies have been mixed. There is some evidence from Germany and the Netherlands, in particular, that a restriction of the use of tetracyclines in feed corresponds with a decrease in the number of resistant strains in swine. But it is also clear that the solution of the antibiotic resistance problem requires more than a simple ban on subtherapeutic use in animal feeds.

The Western European livestock sector, for example, has been able to survive the ban of subtherapeutic use of antibiotics without tumultuous consequences. But a higher incidence of therapeutic uses of antibiotices has been reported. If, in fact, this occurrence were commonplace, the possible, positive benefits to human health would quickly be negated and indeed, the impact on human health could possibly be detrimental, given there is a link.

Another important question and one that must be addressed is, what would be the economic impacts of a ban on the subtherapeutic use of drugs on animal agriculture?

In 1978, the U.S. Senate Committee on Agriculture, Nutrition and Forestry requested the Economics, Statistics and Cooperatives Services (ESCS), of the Department to conduct an assessment of the impacts of the FDA proposals to restrict the use of penicillin, tetracycline and the premixes containing these drugs and banning the use of the nitrofurans.

In addition, a restriction on the use of sulfamethazine in swine feed was included because of the prospect of such a restriction at that time. The analysis included assessment of impacts on the beef, swine, broiler, table eggs, turkey, dairy and sheep sectors as well as on consumers.

Before going further, I should note that because of the assumptions upon which the ESCS study was based do not reflect the restrictions H.R. 7285 might impose—and also do not mirror what would take place in the real world—the results cannot be applied directly to discussion of this measure.

A key assumption—and one that results in overestimation—was that substitutes in the form of other drugs, better management, more sanitary production facilities and other aids, were not used to replace the restricted drugs.

In short, this was part of the worst-case scenario. Still, we believe that study does provide insights as to the importance of subtherapeutic use of antibiotics in animal agriculture and places bounds on the extent of economic and possibly structural impacts.

The ESCS study found that in the first year of the restrictions output of animal products would decrease. Farm prices, food prices and production costs would increase; but net farm income would actually increase because prices would increase more than costs. This would motivate producers to expand output in subsequent years and prices would fall back toward the level that would have prevailed if the restrictions had not been imposed.

Consumer prices for food were estimated to increase between 1.2 and 3.8 percent the first year as the result of higher meat prices, according to the ESCS study. By the fifth year following the restrictions, estimated price increases had moderated to between 0.2 and 0.6 percent over what would have prevailed.

Per capita consumption of livestock products would fall between 7 and about 21 pounds—or 3 and 9 percent, respectively—the first year. By the fifth year after the restrictions are imposed, the reduction would be less severe due to the increase in farm output—between 1.4 and 4.3 pounds or 0.6 and 1.8 percent.

The analysis showed that the food system could largely adjust to extensive changes in the use of our antibacterial drugs—penicillin, tetracycline, nitrofurans and sulfamethazine.

The ESCS study I have referred to also contained recommendations on research needed to fill the voids in knowledge about the safety of antibiotic use.

The recommendations pertain to research on the subtherapeutic use of antibiotics, reducing residues of antibacterials such as sulfonamides in animal tissues, and reducing the incidence of diseases customarily treated by antibiotics that may cause the development of resistant strains of these diseases.

The NAS study also makes specific recommendations for needed research.

From the viewpoint of animal agriculture, we particularly see a need for additional research on mode of action—in other words, learning how and why antibiotics work so that alternative compounds and/or practices might be implemented.

Having addressed aspects of concern to agriculture, I thank you for this opportunity to appear before this subcommittee. We will be happy to respond to any questions that the committee members might have.

Mr. WAXMAN. Thank you very much for your testimony.

Dr. Crawford, what is your current statutory authority regarding antibiotics in animal feed? What actions have you taken to date to restrict their use, and what restrictions have been imposed on you by the Appropriations Committee?

Dr. CRAWFORD. Our current statutory authority enables us to take action against penicillin and the tetracyclines, which we proposed to do in 1977 and early 1978. Since that time, we have not taken actions against these compounds because there is, as you know, a division of opinion about the extent of the risk.

We decided in 1978 to hold evidentiary hearings on these issues. At about the same time the House Appropriations Committee, and then the full Congress, moved to restrict our actions in this area. They stated that we could hold hearings, but we may not take final action until, first, a National Academy of Sciences study was completed. That study, costing approximately $250,000, was completed in March of this year.

As it was being completed, the Appropriations Committee again ordered us not to take final action until, at this point, a large, comprehensive $1.5 million study could be completed to answer what they believed were some gaps in the evidence.

And now there is an interest in extending what is in effect, a moratorium toward taking any final action.

We may go to a hearing but we may not take final action.

Mr. WAXMAN. The report of the National Academy of Sciences recommended that additional studies be conducted. Would you explain what one would learn from these studies and whether we should delay any regulatory action until their completion?

Dr. CRAWFORD. The National Academy of Sciences' report indicated that a large, comprehensive, all-encompassing study would not be technically possible. They studied the issue for approximately 6 months and concluded that the study envisioned by the Congress was not obtainable.

They did suggest that we consider some smaller, discrete studies, to specifically answer gaps in the scientific knowledge regarding this problem.

The Academy, though, finished by saying that even were we to complete these studies, our regulatory position would perhaps be no stronger and probably would not be stronger.

We are in somewhat of a quandary because these studies would cost well over $1 million and yet would not finally answer the regulatory questions.

We have asked the relevant congressional subcommittees for their wisdom in this issue and we have commissioned a broad multidisciplined task force to look at the possibility of doing these smaller and more discrete studies in an effort to learn whether it would be a waste of the taxpayer's money or whether or not it would perhaps add more than the National Academy of Sciences thought it would.

Mr. WAXMAN. Let me invite the others to join in on any of these points I am raising.

Do FDA and the administration believe that the subtherapeutic uses of penicillin and the tetracyclines in animal feed should be prohibited?

Dr. CRAWFORD. Yes.

Mr. WAXMAN. Is that the administration's position?

Dr. CRAWFORD. Yes.

Mr. WAXMAN. Have you looked at the experiences in countries which have restricted the subtherapeutic use of antibiotics in animal feed, and have these experiences indicated that it had any effect on resistance to bacteria or on the economics of the agricultural industry in these countries?

Mr. Hjort?

Mr. HJORT. We have had some reviews, limited reviews, of the experience in western Europe; and as I indicated, the results do appear to be mixed.

In the United Kingdom there appears to be no change in the total quantity of drugs being used. There is evidence in some countries—in Holland, for example—where it appears the resistance to certain strains that was building up has been reduced.

But, as I say, the results so far are very mixed. I think one of the very difficult problems is the relationship to the problems you are addressing at subtherapeutic versus therapeutic use and how one makes that distinction, and to define the same consequences that take place at either one of those levels of usage.

In the United Kingdom experience it appears that some are actually increasing the use above what it previously was.

Ms. Foreman. If I could add to that the Danes have prohibited the subtherapeutic use of antibiotics, and yet the veterinary service in Denmark did express some concern that they have a continuing problem with the prescription of the drugs now at a therapeutic level.

Mr. Waxman. They have not restricted the prescription of drugs for therapeutic uses, only subtherapeutic uses?

Ms. Foreman. They found the elimination of the subtherapeutic use has been somewhat counteracted by a problem with continuing prescriptions. They were not prepared to state that as a serious difficulty, but it was expressed informally as a continuing concern.

Mr. Waxman. Many groups, particularly the livestock producers, have been proceeding under the assumption that subtherapeutic use of antibiotics is effective in disease prevention and growth promotion. Do we have evidence that this is indeed the case?

Mr. Hjort. We do have evidence, considerable evidence, with respect to specific drugs. Much of that evidence goes back to the 1950's and 1960's, but there have been relatively recent studies that show there is a positive response in terms of growth and in terms of disease prevention.

When you get to the general question, then it gets to be much less precise, much more difficult to draw conclusions. As I indicated in my testimony, although not well documented, there are some operations of relatively large size not using these drugs at subtherapeutic levels; some are not using drugs at all, apparently; and yet there is no evidence so far that there has been a major problem.

So, again, as in most of these issues, the record does seem to be mixed. But it is very clear in the early studies that there was a positive impact as far as growth and disease prevention were concerned.

One other point I would make is that it is difficult for us to simply extrapolate from the European experience. By and large they do not have the very large operating units that we do in this country, and so the threat of disease here is considerably greater simply because of the size of the operation.

Mr. Waxman. Dr. Crawford, do you have a different view on that question?

Dr. Crawford. I would just amplify that with the exception of England, I think that the incidence of strains susceptible to these two antibiotics has improved across the board. In the Netherlands and in West Germany the restrictions have been in place for approximately 6 years, and they notice a positive benefit in terms of those strains of salmonella and other enteric organisms now susceptible to penicillin and tetracycline.

In England, as Dr. Hjort mentioned, the position hasn't improved markedly because they have not really restricted the use of these compounds. They have just tranferred the route distribution. They are now calling this month in the British Medical Journal for a reanalysis of the problem and there is some feeling they will take restrictions similar to what we proposed.

Mr. Waxman. I was interested to know your views on the assumptions under which the livestock producers have been working, that in fact the subtherapeutic use of antibiotics is effective in disease?

Dr. **Crawford**. Yes, as Secretary Foreman mentioned, we have approximately 20 feed additive antibiotics that are approved for use; therefore, there are basically 18 substitutes for the 2 we propose to restrict.

The position of the FDA regarding those 18 is that they are, with few exceptions, safe and effective. We do, therefore, concur they are effective in animal agriculture.

We are not attempting to wipe out the use of feed additives and antibiotics. We are talking about penicillin and the tetracyclines.

Mr. **Waxman**. Do you know whether there are any adverse side effects to humans from the drugs that would be substituted were this bill to become law?

Dr. **Crawford**. Most of the newer feed additives and antibiotics are those that are used only in veterinary medicine. Most of them are not absorbed from the gastrointestinal tract and therefore are not subject to residues in edible tissues, and they do not pose, in our opinion, the threat to human health as do penicillin and the tetracyclines.

Mr. **Waxman**. Would the substitute uses have the same resistance problem or would a cross-resistance develop from the substitutes?

Dr. **Crawford**. We do not propose that any antibiotic be approved for use as a feed additive that has cross-resistance to penicillin and the tetracyclines.

Mr. **Waxman**. Do we know, in fact, whether the substitutes are effective in disease prevention and growth promotion?

Dr. **Crawford**. Yes, we believe they are.

Mr. **Waxman**. Does the subtherapeutic use of penicillin and the tetracyclines increase resistance to these drugs in the animals? Have you seen any evidence of that?

Mr. **Hjort**. There apparently is some evidence on that. We do have with us a couple of our scientists who may want to, if you want them to, respond in more detail on that particular question.

Mr. **Waxman**. Let me ask them to furnish something for the record on that point, because I think it would be important for us to know whether the subtherapeutic use of penicillin and the tetracyclines will make it more difficult to treat the animals after they are sick, and whether we see increased resistance in these animals that have been using the drug.

Mr. **Hjort**. One of the questions that continues here is what happens over time. That is part of the question we now are asking. If an animal is receiving the drug, does it become less effective with time?

There does appear to be in some cases some resistance that develops. I think that is clear from the European experience, yet we don't know of any widespread disease outbreaks that have come as the result of developing resistance.

So, again, this is one of those questions, as most of these are, for which there are just no definitive answers, but we will provide more detail for the record.

[The following information was received for the record:]

In feeder cattle antibiotics are used in feed to improve feed conversion and weight gain by reducing the incidence of liver abscesses and by aiding in the maintenance of the animal's general health and controlling subclinical infections.

Appearing before the FDA Subcommittee on the Use of Antibiotics in Animal Feeds (1976), Dr. Flack of Monfort Feedlots, Greely, Colorado, reported on their experience using a feeding level of 70 mg. of chlortetracycline (Aureomycin) per head per day in over five million feeder cattle. After more than 15 years of continuous feed use the antibiotic remains equally effective as a growth stimulant and the preferred therapeutic antibiotic for treatment of sick animals remains oxytetracycline. Thus, there has been no compromise of tetracycline therapy from feed use.

When the 70 mg of chlortetracycline was taken out of the feed experimentally the percent of calves removed from the lots for treatment of disease rose from 4 percent to over 8 percent.

Dr. CRAWFORD. If I might, Mr. Chairman, we would like to add something for the record also. We believe unequivocally that penicillin and the tetracyclines are not as effective as they were when they were first introduced in animal agriculture.

Mr. CARTER. Mr. Chairman, would the gentleman yield on that? Are they as effective on humans now as they were when they were first used?

Dr. CRAWFORD. I believe the incidence of resistant strains has increased over a period of years.

Mr. CARTER. Then there has been no difference. Actually, they are not as useful in humans as they once were?

Dr. CRAWFORD. Yes.

Mr. CARTER. Thank you, Mr. Chairman.

Mr. WAXMAN. Do you know whether we have a greater resistance in animals to these two antibiotics than we have in humans?

Dr. CRAWFORD. Greater than in humans? I would say it would be approximately the same problem.

Mr. WAXMAN. So we just generally have a greater resistance in both humans and animals to these antibiotics?

Dr. CRAWFORD. Yes.

Mr. WAXMAN. And can we discern how much of the resistance in humans is based on the transfer of resistant bacteria from animals to humans, or whether this is based on the use of the antibiotics with humans alone?

Dr. CRAWFORD. This is the great problem the Academy encountered. It is impossible to tag these organisms to tell whether they are of animal origin or of human or whatever origin. Therefore, to answer that question unequivocally is impossible.

Mr. WAXMAN. The 1978 USDA inflation impact statement on the effect of completely banning the subtherapeutic use of antibiotics in animal feeds stated that the economic system would be resilient to a restriction of antibiotic uses. Wouldn't the costs to consumers and to the livestock industry be even less with the use of the substitutes?

Mr. HJORT. Yes, if there were effective substitutes available. As I indicated, these were in effect worst-case scenario estimates, and the major impact would be in the first year, and that impact would rise in its magnitude because of the assumption of no equivalent substitutes.

Mr. WAXMAN. Do you believe there is an equivalent substitute to tetracycline?

Mr. HJORT. I am not sure there is. I simply don't know.

Mr. WAXMAN. Dr. Crawford, do you believe there is?

Dr. CRAWFORD. Yes, there are.

Mr. Waxman. Is it possible the subtherapeutic uses of antibiotics are encouraging poor management practices in the livestock industry? Couldn't such things as improved sanitation and pasture rotation reduce the need for subtherapeutic uses of antibiotics, and wouldn't this further reduce any economic effects?

Mr. Hjort. Well, the major uses are in contained operations, so the rotation of pasture and so on I don't think is a factor. Broiler operations are very intensively managed and they are very sophisticated operations. Cattle feeding operations are similar, and so I don't think the alternatives that you are mentioning would really be applicable in that situation.

The concern in these large operations over any disease outbreak is extremely real, and the operators of these large confined systems are extremely careful with respect to the prevention of disease, and so I think the system, the structure that has developed in part because of the use of these drugs, makes it difficult to think of alternatives.

To go back to small feeding operations, clearly would lead us in the direction of less efficiency.

Mr. Waxman. On page 2 of USDA's inflation impact statement:

> These results do not take into account any changes in the structure of production agriculture that might accompany an animal drug ban. Increased risks associated with the feeding of poultry and livestock in confinement without the low-level use of animal drugs could make such confinement production systems less viable and change the magnitude of this result.
>
> On the other hand, we were not able to measure the effect of changes in management practices that might occur in anticipation of or following the enactment of such a rule. Improved sanitation and pasture rotation could reduce the magnitude of even the first year effect, as we have shown them.

So, I gather what you are saying is that because of the use of subtherapeutic doses of anitibiotics we are not trying some of these ways that may be more efficient and therefore diminish the impact of any ban on the use of these antibiotics?

Mr. Hjort. I think in that one statement there are two different kinds of systems that are being talked about. In the confined operation you have one set of circumstances. If it is a ranch operation where usually they are not feeding but they are just maintaining their herds and so on, and so it is not a question there.

Mr. Carter. Usually they raise feeder cattle?

Mr. Hjort. The feeder cattle operation, yes.

Mr. Waxman. From the experiences of other countries that have restricted the subtherapeutic uses of antibiotics, have we seen a decrease in resistance? Dr. Crawford?

Mr. Hjort. As has been indicated, in Germany and Holland the evidence appears to be that, particularly in hogs, the build up of the resistance has come on down. That is the only evidence of it that I know of, but it has been reported in Holland and in Germany. That appears to be the result with swine.

Mr. Waxman. Has either FDA or USDA done an economic analysis that would include the use of substitutes should this bill become law? And if you haven't, can such analysis be done for us?

Dr. Crawford. Yes, the USDA study, as Dr. Hjort mentioned, did not take into consideration substitutes, and we will be preparing such an assessment and will supply to the subcommittee if you so desire.

Mr. WAXMAN. Dr. Carter?

Mr. CARTER. Thank you, Mr. Chairman.

You mentioned the ban of subtherapeutic antibiotics in England?

Dr. CRAWFORD. Yes.

Mr. CARTER. I suppose that resulted in less use of those antibiotics?

Dr. CRAWFORD. No, sir; they put in an elaborate system of requiring veterinary prescriptions. There was an initial diminution, but after 10 years the usage level is approximately what it was prior to the restrictions.

Mr. CARTER. I believe that is a little bit on the offside. The amounts are essentially double; penicillin is, and tetracycline, and other antibiotics by 1975 didn't remain the same, but doubled.

That means, of course, there would be really a number of resistant strains, more of it, if the flora of the gut were the same in the human as it is in the hog or cow or in a chicken, which really it isn't. The flora is different, is it not?

Dr. CRAWFORD. Yes, it is.

Mr. CARTER. Since we get these resistant E. coli—now, E. Coli is not particularly a pathogenic organism in most cases, but we get them—how would the human get this particular strain of bacteria? How would he pick it up? How would he or she pick it up?

Dr. CRAWFORD. Through animal contact or contamination of the food supplies.

Mr. CARTER. Don't they cook their food?

Dr. CRAWFORD. In most instances.

Mr. CARTER. And it would be very poor sanitation, wouldn't it, and not much chance of transfer, as I see it, of E. coli from a beef animal to a human, except through poor sanitation.

Are there any antibiotics used in animals that are not used in humans?

Dr. CRAWFORD. Yes.

Mr. CARTER. And what about flavomycin?

Dr. CRAWFORD. It is an antibiotic used in veterinary medicine, not used in human medicine.

Mr. CARTER. For what use?

Dr. CRAWFORD. For growth production and feed efficiency.

Mr. CARTER. Do you propose a ban on the use of flavomycin?

Dr. CRAWFORD. No.

Mr. CARTER. When did we note the resistance to antibiotics begin? Did it begin with animal feeding or did it begin before?

Dr. CRAWFORD. In veterinary medicine the use of antibiotics coincided——

Mr. CARTER. I didn't say the use but the resistance of bacteria.

Dr. CRAWFORD. The resistance began appearing even before the use, and certainly shortly after the use.

Mr. CARTER. Even soon after the development of penicillin, which was first used, I believe, in 1943, and really invented by 1927, as I recall, correct?

Dr. CRAWFORD. It was invented in 1928 by Alexander Flemming.

Mr. CARTER. 1927?

Dr. CRAWFORD. And rounding that off, Mr. Carter, I would agree with you.

Mr. **Carter**. All right, sir. It took 16 years for us to use this wonderful drug, but shortly after that we found that certain bacteria became resistant to it; isn't that correct?

Dr. **Crawford**. Yes.

Mr. **Carter**. Within a short while—and we have resistant strains in humans now, because tetracyclines are commonly used; is that not correct?

Dr. **Crawford**. Yes.

Mr. **Carter**. Not only would there theoretically be a transference of these resistant strains from cattle and so on, but we ourselves, or rather the bacteria with which we become infected, also have developed a resistance, and it has gone back to soon after the discovery of these different antibiotics.

What is your basis for saying that we should limit the amount of penicillin to 500 parts per million in animal production?

Dr. **Crawford**. That would basically take care of those uses that are now approved.

Mr. **Carter**. What was the basis for your arriving at this level of 500 parts per million? How did you reach that?

Dr. **Crawford**. We reached that basically because our experience over time had shown that the use of penicillin at the approved levels resulted in resistant strains.

Mr. **Carter**. Well, this means a level of antibiotics permitted in the meat when it is sold. Of course, you do recommend, I believe, that cattle be taken off of penicillin for how many days before they are slaughtered?

Dr. **Crawford**. Penicillin shows little tendency to persist. It is very short; and there are no cattle uses. It is used primarily in swine.

Mr. **Carter**. Yes, primarily, but it can be used in all animals?

Dr. **Crawford**. Yes.

Mr. **Carter**. You do recognize the fact that the flora of the gut of animals is different from the flora of the gut of humans; is that correct?

Dr. **Crawford**. Yes.

Mr. **Carter**. And that really to get those bacteria, humans would have to contaminate themselves with the bacteria coming from the gut—the bacteria that were resistant to antibiotics; is that correct?

Dr. **Crawford**. Correct.

Mr. **Carter**. Well, improperly cooked food would be a way. Actually, if this person used good sanitation there would be no danger.

I am interested, Ms. Foreman, in your name "Tucker." Where did you get that name?

Ms. **Foreman**. From my father.

Mr. **Carter**. I don't know of a better place to get it.

Ms. **Foreman**. It is preferred.

Mr. **Carter**. Where was he from?

Ms. **Foreman**. Arkansas.

Mr. **Carter**. My mother happened to be a Tucker. She is from Tennessee.

Thank you.

Mr. **Waxman**. Well, let's don't leave it there.

Ms. **Foreman**. Some of us couldn't make a living in Tennessee and we went on down to Arkansas.

Mr. **Carter**. That was our trouble.

Mr. **Waxman**. Mr. Devine.

Mr. **Devine**. With my limited legal education, I can't engage in these medical discussions with any accuracy. I have no questions.

Ms. **Foreman**. Mr. Waxman, if I could just respond very briefly to Congressman Carter's comments about the proper cooking of food, I think that certainly the point is a very valid one, and yet the Congress in enacting the meat and poultry inspection laws under which we operate have required the Government to enforce sanitation that would eliminate, that would attempt to deal with, the problem even if the food were not adequately cooked, and I wouldn't want the Congress to be on record that somehow it is totally incumbent upon the public, and no responsibility of the producer or the Government to put food on the shelves that is not contaminated.

The customer, obviously, has an obligation—the public—to prepare food adequately, and yet I am sure you didn't intend to withdraw from the longstanding commitment of the Congress and the Government to require producers to put food on the shelves that is not contaminated.

Mr. **Carter**. Far be it from me, young lady. I have always supported sanitation, as you know.

Ms. **Foreman**. Yes, I do know.

Mr. **Carter**. For the past many years and I will continue to do it.

Ms. **Foreman**. Because I think that to a certain extent the concern about the contamination from subtherapeutic uses of antibiotics is a natural outgrowth with the development of additional scientific knowledge of the concern we have traditionally had about the contamination of food by more ordinary contaminants, by feces or by other means of contamination.

Mr. **Carter**. But even still, even then, with the best that we can do—and I have voted for every bit of legislation over the years to promote and attempt to provide sanitation of our food—still there is a factor in there, I regret to say—this doesn't come from legislation; this comes from the Executive Department—people have contamination in many, many foods; is that not true?

Ms. **Foreman**. Yes.

Mr. **Carter**. What are you going to do about it, to get rid of it?

Ms. **Foreman**. Well, we are trying very hard to get rid of it.

Mr. **Carter**. Well, let's get rid of that fecal contamination.

Thank you very much.

Mr. **Waxman**. Let me ask this question: Would you agree with the statement that the dangers to people from transfer of resistant bacteria from animals are eliminated if there is proper sanitary handling of the food and proper preparation of the food? Is that a scientifically accurate statement?

Ms. **Foreman**. Not to my knowledge.

Dr. **Crawford**. I could not totally agree with that. I think the more unsanitary it is, the more likely for transmission. I wouldn't disagree with that.

Mr. **Waxman**. Well, transmission is still possible even using accepted sanitary ways of handling prepared foods, correct?

Ms. Foreman. I think that question is rather complex and deserves an answer that none of us would feel quite prepared to give you; but I think we can give it to you for the record.

Mr. Waxman. Well, let's leave the record open and we would appreciate an answer.

[The following information was received for the record:]

Raw meat and poultry prepared under sanitary conditions and properly refrigerated are never devoid of microoganisms. These foods have in indigenous low level of microoganisms which are resistant to normal cooking temperatures. Although routine cooking eliminates most microoganisms from meat products, the cooked food is not sterile unless is is subjected to a lengthy, high-temperature process, like canning, which destroys bacterial spores. Therefore it is possible for cooked foods to contain some bacteria.

Moreover, homemakers sometimes inadvertantly or through ignorance of sanitary food practice compound this situation by placing cooked meat on dishes which are improperly sanitized—causing recontamination of the food. If inadequate cooking procedures are followed at this point, the bacteria, including any resistant microoganisms present, will florish. Eating this recontaminated food will increase the resistant bacteria in the person's body. If that person then becomes ill and requires antibiotic therapy, there is a greater possibility that routine antibiotic therapy will not produce the usual result, because the patient has elevated numbers of resistant bacteria. Of course, other antibiotics can be used to control the illness.

Mr. Carter. Mr. Chairman, have there been major disease outbreaks that have shown penicillin and tetracycline to be less effective in fighting diseases than in earlier times?

Mr. Hjort. Not to our knowledge.

Mr. Carter. Thank you very kindly.

Mr. Waxman. Well, we would appreciate any other comments or thoughts that you might have in light of the questions and the discussion we have had in our hearings.

We will leave the record open for that purpose.

I want to thank you very much for being here.

[The following statements and letters were received for the record:]

STATEMENT
# of the
NATIONAL CATTLEMEN'S ASSOCIATION

The "Antibiotics Prevention Act," H.R. 7285, is untimely, inappropriate and directly conflicts with the current regulatory process already in place and operating at the Food and Drug Administration. It is unnecessary because it adds yet another layer of bureaucratic regulation to FDA's existing sufficient authority, and is intervention by Congress into a proceeding already begun by FDA.

This proposed legislation would amend the Federal Food, Drug and Cosmetic Act to limit the antibiotic drugs which may be used in subtherapeutic doses in animal feed. But the Act already provides for FDA regulation of drugs added to animal feeds. The Act also provides mechanisms to remove drugs from the market and subsequently from use in animals. If the Secretary finds an imminent hazard to human health, an animal drug approval may be withdrawn in advance of an FDA hearing. No such imminent hazard has been found with the use of subtherapeutic level animal drugs in feeds, and FDA has clearly stated that formal evidentiary hearings will be held on this issue once the research mandated by Congress has been reported.

This Congressional research mandate was contained in both Senate and House Reports which accompanied H.R. 4387, the Agriculture, Rural Development and Related Agencies Appropriation Bill, 1980. Thus, it appears the Committee on Interstate and Foreign Commerce, should they favorably report this Bill, will be in direct conflict with previous actions of the Committee on Appropriations.

The Food and Drug Administration has, for several years, proposed the elimination of most low level uses of antibiotics in livestock feeds. This is being done on grounds that such uses of antibiotics theoretically may result in the transfer of antibiotic resistance from animals to humans--thereby making antibiotics less effective in treating bacterial infections in humans.

One question becomes paramount to the human health issue. What is the route of transmission of resistant bacterial strains from animals to man? Only a very minor portion of our population ever comes into direct contact with food animals, either at the farm level or at the packing plant. Therefore, proper meat sanitation and proper food preparation become key issues to this debate. With one of the best government meat inspection programs in the world, the U.S. does indeed assure the general public of a clean, wholesome domestic meat supply. Reports of improper meat preparation are almost non-existant. What, then, is the real or the theoretical route of resistance transmission?

FDA's proposal would ban the principal uses of antibiotics in feedlot and other feeds for cattle--including growth promotion and feed efficiency, prevention of respiratory disorders and shipping fever, and prevention of liver abscesses and certain other problems. Still permitted would be certain therapeutic feed uses for anaplasmosis, pneumonia and shipping fever, and bacterial enteritis. Under this bill however, such important uses to the cattle industry such as prevention of shipping fever and anaplasmosis could easily be denied.

Former FDA commissioner Kennedy acknowledged that FDA's position is based on theory, not on actual evidence of disease problems in humans. Congress should oppose actions based on supposition, and support a thorough study to determine whether there is in fact a definite and harmful relationship between human health and the feeding of animal drugs to livestock.

The cattle industry also feels that any future requirement to limit these antibiotics (and ultimately other drugs) to use only on a veterinarian's prescription would represent needless and costly interference with efficient livestock production.

The government's own data have shown that the proposed ban would have a severe economic impact on both producers and consumers of meat.

There has been a great deal of research on antibiotic resistance. But the conclusion that animal use causes disease problems in humans seems to be one of assumption, not documented fact. A 25-year record of safety and efficacy appears to have been ignored.

If the claims now made by FDA were really valid, animals no longer would respond to antibiotics. But the fact is that animals do respond, even on premises where antibiotics have been fed for years. Secondly, if there really were a human disease problem, those who work with animals should be the first to experience it.

Obviously, cattlemen are consumers as well as producers, and they do not want to endanger their families or employees or the consumers who buy their product. But, at this point, the questions raised by FDA appear to be largely academic. Before any further action is taken, there can and should be epidemiological (population) studies to see whether antibiotic feeding really does cause any health problems--among those who work with animals and/or those who eat meat.

If the government were to apply the idea of theoretical risk to all technical products--without valid scientific evidence to support its position--the continued use of many animal drugs and other valuable production tools would be jeopardized. Thirty years of technological progress in agriculture would be nullified.

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STATEMENT
of the
NATIONAL CATTLEMEN'S ASSOCIATION
Before The
SUBCOMMITTEE ON HEALTH AND THE ENVIRONMENT
Of The
HOUSE COMMITTEE ON INTERSTATE AND FOREIGN COMMERCE

Relative To

H.R. 7285, "ANTIBIOTICS PRESERVATION ACT"

JUNE 12 and 24, 1980

The "Antibiotics Prevention Act," H.R. 7285, is untimely, inappropriate and directly conflicts with the current regulatory process already in place and operating at the Food and Drug Administration. It is unnecessary because it adds yet another layer of bureaucratic regulation to FDA's existing sufficient authority, and is intervention by Congress into a proceeding already begun by FDA.

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If the government were to apply the idea of theoretical risk to all technical products--without valid scientific evidence to support its position--the continued use of many animal drugs and other valuable production tools would be jeopardized. Thirty years of technological progress in agriculture would be nullified.

SUPPLEMENTARY STATEMENT
OF
RACHELLE LABORATORIES, INC.
ON H.R. 7285, "ANTIBIOTICS PRESERVATION ACT"
BEFORE THE
SUBCOMMITTEE ON HEALTH AND ENVIRONMENT
OF THE
HOUSE COMMITTEE ON INTERSTATE AND FOREIGN COMMERCE
JULY 3, 1980

Rachelle Laboratories, Inc. ("Rachelle") is a manufacturer of tetracycline and penicillin products for use in animal feeds. Rachelle currently holds approved new animal drug applications ("NADA's") for these products. We appreciate the opportunity to supplement the record before this Committee with our views on H.R. 7285.

It is Rachelle's position, both from its long standing interest in the safety of antibiotics in animal feeds and from reviewing the testimony already presented at these hearings, that enactment of H.R. 7285 represents an unnecessary and inappropriate legislative intrusion into an existing and fully adequate regulatory system that FDA is already implementing.

Before turning to our specific objections to the effect of H.R. 7285, we would like to take strong exception to certain findings contained in Section 2 of the Bill. This section assumes as true certain scientific hypotheses that are, in fact, far from certain. As was amply demonstrated by much of the testimony before this Committee, the risks to human health from the subtherapeutic use of penicillin and tetracycline in animal feed are wholly theoretical and some of the scientific premises on which these postulated risks are based, such as the ability of animal bacteria to colonize in the human, are still highly controversial. Similarly, the effectiveness of the restrictions imposed in European countries and the availability of safe and effective substitutes are also open to question. The statements delivered by Dr. Hewitt on U.C.L.A., Dr. Finkel of the AMA and Dr. Hjort of the Department of Agriculture indicate quite clearly that the issues surrounding the use of antibiotics in animal feed do not lend themselves to solution by legislative fiat, but rather require careful scientific evaluation where all sides can present their data and views and where the risks and benefits can be fully and openly examined.

As discussed below, this is exactly the course that the Food and Drug Administration has wisely chosen to take in ordering formal evidentiary hearings on these products. To attempt to short circuit the full administrative process already set in motion would be, we believe, both unwise and unfair to the manufacturers, the farmers and the public all of whom have a vital interest in resolving the important issues raised by the authors of H.R. 7285.

One point that we believe was clearly demonstrated at the Hearings before this Committee and, indeed, was virtually uncontested, is that the Food and Drug Administration has more than ample authority to deal with the concerns raised by H.R. 7285. The Federal Food, Drug, and Cosmetic Act (the "Act") provides a comprehensive mechanism for the regulation of drugs added to animal feeds. Under Section 512 of the Act, it is unlawful to market any new animal drug other than in accordance with the approval of the drug by the Food and Drug Administration. Furthermore, the use of the drug by feed mills and livestock handlers must also be in accordance with additional FDA approvals.

The Act requires that the manufacturer demonstrate both the safety and the efficacy of the new animal drug, and the Act specifically provides that "The term safe . . . has reference to the health of man or animal." Section 201(u). Thus, in approving new animal drugs, the Commissioner must specifically find that the use of the drug is safe with respect to the health of man as well as the animals to which the drug is to be administered. The Act also prescribes stringent tests to be met by the applicant in demonstrating the safety of the drug to man or animals. See Sections 512(d)(1)(A), (B) and (2). Moreover, FDA is empowered to revoke the approval if it finds that "new evidence ... evaluated together with evidence available...when the application was approved, shows that such drug is not shown to be safe for use. . ." Section 512(e)(1)(B).

Normally, FDA is required to provide notice and opportunity for hearing before revoking an approval for any new animal drug. See Section 512(e)(1). Where the Secretary of Health and Human Services "finds that there is an imminent hazard to health of man", he may withdraw a new animal drug approval in advance of an FDA hearing. Section 512(e)(1).

Congress has thus provided comprehensive authority under the Act to take into account human health as a controlling factor in both the approval and disapproval of new animal drugs, and has given the Secretary authority to suspend new animal drug approvals in the event of an imminent hazard to the health of man. Under these circumstances, we believe that the proposed legislation adds simply a superfluous layer of regulatory activity to FDA's already abundant authority to control the use of antibiotics based on any purported hazard to the health of man resulting from use of these drugs in animal feed.

The testimony before this Committee also demonstrated that the Food and Drug Administration currently is using this authority to deal with the very concerns addressed by H.R. 7285.

FDA, by notices of opportunity for hearing published in the Federal Register on August 30, 1977 (42 Fed. Reg. 43772) and October 21, 1977 (42 Fed. Reg. 56264), has already begun the process provided by the existing statute for restricting the uses of these previously approved drugs. The companies involved, including Rachelle, have responded to that proposal by demanding a hearing, and FDA has indicated its willingness and intention to hold a hearing. See 43 Fed. Reg.53827 (November 17, 1978). We believe it is particularly inappropriate to contemplate legislation that would initiate new regulatory procedures while statutory proceedings involving the very same issues are underway.

Considerable FDA expertise and manpower are now at work on the issues raised by the use of low levels of antibiotics in animal feeds. The personnel involved in these matters are those in the Bureaus of Veterinary Medicine and Foods, to whom the Commissioner has assigned responsibility for evaluating the public health risks of the low level use of antibiotics in animal feed. The proposed legislation would direct a third FDA operating unit, the Bureau of Drugs, to undertake essentially a separate, but identical, review and determination of these issues in order to advise the Commissioner in issuing regulations under Section 507 of the Act, as it would be amended by H.R. 7285. This could present problems of prejudgment on the part of the Commissioner in passing on rulemaking required by H.R. 7285, and thus potentially compromise the hearing process that FDA has begun under existing statutory authority.

In short, Rachelle believes that existing authority and FDA procedures are adequate to deal with the concerns addressed by H.R. 7285. For this reason we oppose H.R. 7285 as unwise and unnecessary.

NATIONAL PORK PRODUCERS COUNCIL
P.O. BOX 10383, DES MOINES, IOWA 50306, PH 515-223-2600

STATEMENT TO
REP. HENRY WAXMAN
CHAIRMAN
SUB-COMMITTEE ON HEALTH AND THE ENVIRONMENT
INTERSTATE AND FOREIGN COMMERCE COMMITTEE
ON H.R. 7285
THURSDAY, JUNE 12, 1980
BY THE
NATIONAL PORK PRODUCERS COUNCIL

Mr. Chairman and Members of the Committee:

We understand, although we have not received official notification, that the sub-committee you chair is holding hearings on H.R. 7285 on June 12. This bill would increase the authority of the Food and Drug Administration (FDA) to restrict the use of antibiotics, at sub-therapeutic levels, in animal feeds. We do not believe that this legislation is desirable, or even necessary, and therefore, should not occupy the time of your sub-committee or Members of Congress.

Let me explain our views on this bill. First, the entire subject of the use of antibacterials has been under intense study by the FDA for 10 years or more. During 1970-72, the FDA had a 15-member task force that reviewed this practice and made recommendations which the agency pursued. In the mid-70's, FDA again had this practice studied comprehensively by a sub-committee of its national advisory committee and later the parent committee itself. As a result of these studies, the FDA proposed to restrict the use of penicillin and the tetracyclines in feed to only therapeutic levels. Public and Congressional hearings were held on these proposals. The committees on agriculture of the House of Representatives and Senate properly exercised their overview, a matter that is clearly within their jurisdiction, and the sub-committee on Appropriations for Agriculture and Related Agencies has twice mandated studies on this practice. The first of these studies conducted by the National Academy of Sciences (NAS) found no conclusive evidence that there was a hazard to human health that could be attributed to the use of antibiotics at sub-therapeutic levels in feed. This report stated that research to show conclusively that there was such a hazard can probably not be done. This NAS report also stated that this lack of evidence should not be taken as a guarantee that no hazards exist. This statement is typical of the critics of many important agricultural technologies and further demonstrates the impossibility of proving a negative. FDA has repeatedly stated that there is no clinical evidence, only scattered research reports of such hazard under experimental conditions.

Furthermore, the Office of Technology Assessment (OTA) spent about two years studying this entire matter and that report was inconclusive, too. It, too, referred to the potential or theoretical hazard without any solid evidence that human health was being jeopardized by this practice.

As a result of 10 years of studies by expert committees, Congressional Hearings, studies by such distinguished organizations as OTA and NAS and numerous symposia and seminars held by recognized scientific associations, there is no clear evidence that the feeding of antibiotics to animals creates or presents a danger to human health. This is why we sincerely question the involvement of this sub-committee in this practice at this time.

Furthermore, the second of the research studies which has been mandated by the Congress as a part of the appropriations bill for FDA for Fiscal Year 1980 has not been designed as yet. This study will undoubtedly require two or more years to be completed and analyzed. For this committee to consider legislation to in some way interfere with this procedure is particularly objectionable. If there was any solid evidence of a human health problem, or if FDA had indicated any lack of authority to control the uses of antibiotics in feed, there might be some useful purpose served by consideration of H.R. 7285. Since neither premise exists, we can only consider that the holding of this hearing at this time is requiring the time and attention of Congressmen and staff which could be better utilized addressing the many pressing, critically important national problems facing this nation and the Congress.

This hearing on this bill at this time is particularly objectionable to the nation's pork producers because of the economic crisis this industry is currently experiencing. At current prices for live hogs, our pork producers are losing $25 each time a pig is raised, fed and sent to market. This loss is occurring with the technological tools we desparately need available. Feeding of antibiotics to pigs is one valuable production tool we cannot afford to lose. Unfavorable publicity for our products, just when we are trying desperately to encourage the consumption of pork which is currently a "best buy" economically and nutritionally, is the last thing we need. Providing a public platform for misguided activists to make unfounded charges is a distinct disservice to not only the pork producers but all animal food producers in the U.S., and the U.S. consumer.

While we did not ask for the opportunity to present this statement to the sub-committee, mainly because we do not consider it to be a good use of our time or the Members on the sub-committee, we do request that this statement be made part of the official record of the hearing.

Respectfully submitted,
William C. Buller, President
National Pork Producers Council

Statement of
Charles Henry Hassebrook
Center for Rural Affairs
Walthill, Nebraska

before the

House Subcommittee on Interstate and Foreign Commerce
Subcommittee on Health and Environment

The Center for Rural Affairs is a non-profit, unaffiliated organization based in Walthill, Nebraska. We have monitored structural change in the hog production industry since 1974 when we published the first verion of our report "Who Will Sit Up With the Corporate Sow?". We recently published our fourth update of that report in addition to numerous reports on the role of public policy in fostering concentration in the hog industry. We appreciate the invitation to discuss the impact of restrictions on subtherapeutic antibiotic use on the structure of the hog industry. However, we take no position on this legislation. Its merit must be decided on a range of questions much broader than structural impacts, to which we will limit our comments.

Many more hog producers are threatened by restructuring in the direction of greater concentration, than are threatened by potential dispersion stimulated by limitations on antibiotic use. In fact, restricting antibiotic use would likely minimize structural change and displacement, by preventing concentration in very antibiotic-dependent large scale units. The majority of hogs are still produced by relatively small and moderate sized farms which could adapt to antibiotic restrictions. However, that adaptability and smaller producers may not survive long given a continuation of current trends.

STRUCTURAL CHANGE IN THE HOG PRODUCTION INDUSTRY

The hog industry is in the midst of rapid structural change. The number of hog producers has declined by 80 percent in the last 30 years. USDA predicts a decline of 80 percent in the number of pork producers in just 20 years. (Van Arsdall). Our research in Nebraska has disclosed a rapid trend toward a non-family farm structure. In 1974 approximately 7% of the state's feeder pig crop was produced in corporate or cooperative hog factories, owned by groups of farm and non-farm investors and operated by employees. By 1979 that share had mushroomed to nearly one fourth. Last year, growth among the largest four percent of the nation's hog producers accounted for over two thirds of the dramatic growth in hog numbers which has glutted the market forcing prices to less than half of their recent highs. This condition will be corrected only by the departure of a significant number of producers from the industry. This structural change has been made possible by confinement production techniques, a key component of which is subtherapeutic antibiotic use.

WHAT IS CONFINEMENT TECHNOLOGY AND HOW IS IT RELATED TO SUBTHERAPEUTIC ANTIBIOTIC USE?

Confinement hog production refers to a system in which hogs are confined within facilities for the entire production process. These systems are generally of a much larger than average scale and are equipped with modern labor-saving features.

Subtherapeutic antibiotic use is generally considered the key technological breakthrough making large scale confinement hog production possible. To quote the scientific community:

> "Action that would ban or restrict usage of antibiotics represents one of the few factors that would inhibit trends toward larger and more industrialized hog units."
> Technology Assessment of Integration of the Hog-Pork Industry
> National Science Foundation - July 8, 1977

> "The economics of producing swine and poultry in large confinement units is generally considered strongly dependent on prophylactic feeding of antibiotics to control diseases."
> Use of Antibiotics in Animal Feeds
> An interim summary presented to the Food and Drug Administration by the Council on Agricultural Science and Technology (CAST)

Putting a large number of animals in a single production unit exposes producers to the risk of enormous losses, should a disease gain a foothold and spread through the entire herd. The high cost of confinement facilities requires a higher degree of crowding to achieve the volume necessary to justify the investment. Higher crowding means higher stress and higher disease risk. Large scale confinement producers generally use early weaning systems, in which baby pigs are removed from their mothers at an early age. This technique allows more litters to be passed through a facility in a given time, allowing the necessary volume to justify the high cost of confinement facilities. Early weaning exposes baby pigs to weaning stress at a younger weaker age and deprives pigs of the natural antibodies contained in their mothers' milk, thus requiring antibiotic additives. The confinement technique of passing as many litters as possible through a single facility also increases the need for antibiotics by providing a steady supply of vulnerable young pigs in which diseases can remain alive and multiply. Even with current antibiotic use, large scale confinement systems have brought higher death losses to the hog industry ("Hogs", Another Revolution in U.S. Farming?, USDA).

IMPACT ON STRUCTURAL CHANGE

The entrance of new large scale producers to the hog industry would likely be impeded by the proposed restrictions. Existing large scale producers would probably reduce production. Efforts to reduce disease risk by limiting crowding and weaning pigs at older ages would reduce facility capacity. The degree of these impacts would be affected by the availability of substitutes.

Concern has been raised that restrictions on subtherapeutic antibiotic use could cause a major restructuring of the hog industry, back to very small inefficient units producing only seasonally on pasture, resulting in irregular supplies of market hogs to packers and pork to consumers. We find no basis for these concerns.

Sixty percent of the nation's hogs are still produced in units marketing fewer than 1,000 head per year. Generally, these producers are not using total confinement facilities. Although many of these small and moderate scale producers are currently feeding antibiotics, they could effectively adapt to restrictions.

Irregular seasonal pork production is not the only alternative to large scale confinement hog production. A large part of the nation's pig crop comes from small and moderate scale producers using barns in which pigs are produced year round. These generally are older facilities, of which there is a surplus in farm areas, available at a very low opportunity cost. Although such facilities can not be well adapted to large scale production, they are appropriate to smaller producers and could be used effectively without subtherapeutic antibiotic use. Their low cost makes antibiotic-dependent crowding and early weaning unnecessary and uneconomical.

IMPACT ON PRODUCTION EFFICIENCY

We see no basis for the claim that the small and moderate scale producers whose position would be preserved by antibiotic restrictions are less efficient than large scale producers and costly to consumers.

To quote Secretary of Agriculture Bergland, "The most efficient hog producer today is not some guy who's got a $300,000 modern, sophisticated apparatus. . . . The most efficient in terms of cost is the guy who's sitting out there with an old fashioned system that's all paid for." (Newsweek, June 2, 1980). The only efficiency enjoyed by the large scale operations is in labor use, hardly a priority in a nation with persistent unemployment problems. This comes at the cost of energy intensiveness, a serious problem in a world facing scarce and uncertain energy supplies. The primary force behind the rapid concentration in the hog industry is not economies of scale, but income tax subsidies which return high income investors up to 80 percent of their confinement facility investment in tax savings. Economic impact analyses which assign increased pork prices to the structural impact of antibiotic restrictions, should be re-examined.

SOCIAL IMPACTS

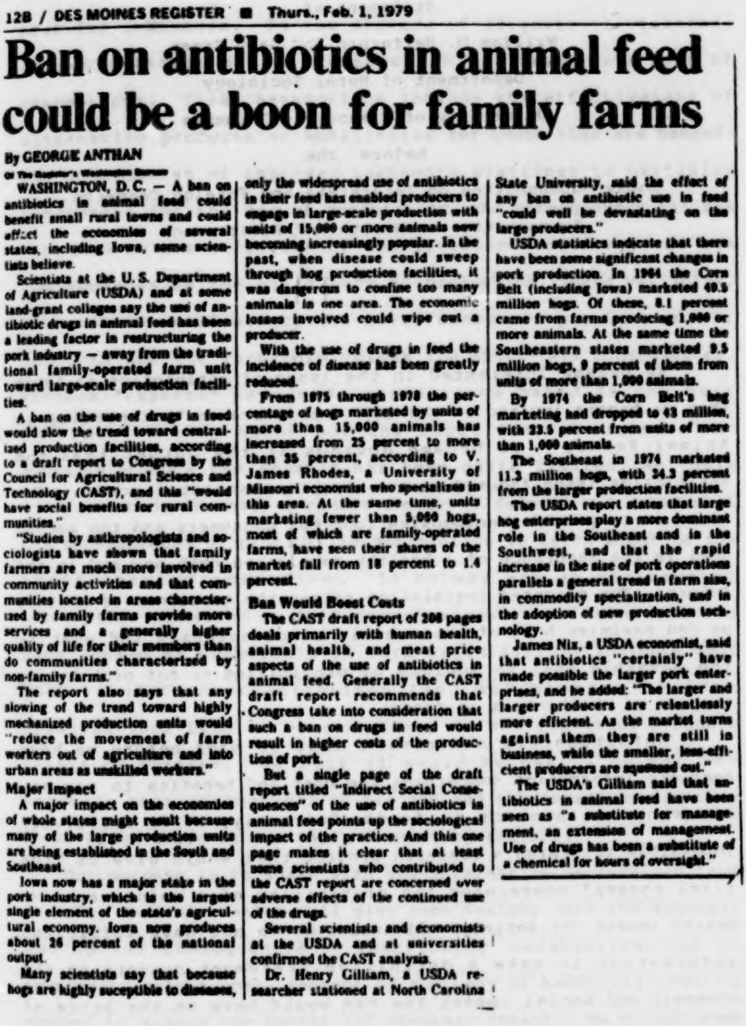
Preservation of opportunity for small and moderate scale hog production would have substantial positive impacts on rural communities. Because of the low investment, high labor nature of smaller hog production systems, they have been the opportunity crop for the non wealthy farmers. Hog production has been the first step on the ladder of farm success, enabling the small and beginning farmer to build equity, establish himself in farming, and purchase land. If the hog industry becomes concentrated, dispersed land ownership will receive a blow. Farm opportunity would become even more limited to a select few of wealthy farmers.

Secretary of Agriculture Bob Bergland has publicly recognized the costs of continuing the trend toward large scale food production. In an address calling for a national dialogue on the future structure of agriculture Bergland noted "With the decline in the number of farms and the number of farm people, we've seen a deterioration of many rural communities. . . . A distortion has taken place in the traditional rural social order. Something has been lost. Something of lasting worth.

This impact will be felt beyond the farm sector. The landmark study, Agribusiness and the Rural Community, often called the Arvin - Dinuba study after the two California communities on which it was based, reveals the positive impact on rural communities of dispersed farm ownership. The study compared two communities, strikingly similiar in most characteristics except that one was economically based on large scale agriculture and the other on more modest sized operations. The small farm community supported significantly more businesses and people at a higher standard of living than did the large farm community. The small farm community had more and superior, community facilities and institutions and was governed in a more democratic manner.

SUMMARY

We foresee no adverse structural impact on the hog production industry from the limitations on subtherapeutic antibiotic use proposed in this legislation. Although such action would cause hardships for large antibiotic dependent producers, its overall impact would be to prevent a major restructuring and preserve economic opportunity for the small and moderate scale segment of the hog industry. By preserving economic opportunity for these farmers, antiobiotic restrictions would likely have a secondary impact of enhancing the economic and social vitality of country towns and rural communties.



12B / DES MOINES REGISTER ■ Thurs., Feb. 1, 1979

Ban on antibiotics in animal feed could be a boon for family farms

By GEORGE ANTHAN

Of The Register's Washington Bureau

WASHINGTON, D.C. — A ban on antibiotics in animal feed could benefit small rural towns and could affect the economies of several states, including Iowa, some scientists believe.

Scientists at the U.S. Department of Agriculture (USDA) and at some land-grant colleges say the use of antibiotic drugs in animal feed has been a leading factor in restructuring the pork industry — away from the traditional family-operated farm unit toward large-scale production facilities.

A ban on the use of drugs in feed would slow the trend toward centralized production facilities, according to a draft report to Congress by the Council for Agricultural Science and Technology (CAST), and this "would have social benefits for rural communities."

"Studies by anthropologists and sociologists have shown that family farmers are much more involved in community activities and that communities located in areas characterized by family farms provide more services and a generally higher quality of life for their members than do communities characterized by non-family farms."

The report also says that any slowing of the trend toward highly mechanized production units would "reduce the movement of farm workers out of agriculture and into urban areas as unskilled workers."

Major Impact

A major impact on the economies of whole states might result because many of the large production units are being established in the South and Southeast.

Iowa now has a major stake in the pork industry, which is the largest single element of the state's agricultural economy. Iowa now produces about 28 percent of the national output.

Many scientists say that because hogs are highly suceptible to diseases, only the widespread use of antibiotics in their feed has enabled producers to engage in large-scale production with units of 15,000 or more animals now becoming increasingly popular. In the past, when disease could sweep through hog production facilities, it was dangerous to confine too many animals in one area. The economic losses involved could wipe out a producer.

With the use of drugs in feed the incidence of disease has been greatly reduced.

From 1975 through 1978 the percentage of hogs marketed by units of more than 15,000 animals has increased from 25 percent to more than 35 percent, according to V. James Rhodes, a University of Missouri economist who specializes in this area. At the same time, units marketing fewer than 5,000 hogs, most of which are family-operated farms, have seen their shares of the market fall from 18 percent to 1.4 percent.

Ban Would Boost Costs

The CAST draft report of 208 pages deals primarily with human health, animal health, and meat price aspects of the use of antibiotics in animal feed. Generally the CAST draft report recommends that Congress take into consideration that such a ban on drugs in feed would result in higher costs of the production of pork.

But a single page of the draft report titled "Indirect Social Consequences" of the use of antibiotics in animal feed points up the sociological impact of the practice. And this one page makes it clear that at least some scientists who contributed to the CAST report are concerned over adverse effects of the continued use of the drugs.

Several scientists and economists at the USDA and at universities confirmed the CAST analysis.

Dr. Henry Gilliam, a USDA researcher stationed at North Carolina State University, said the effect of any ban on antibiotic use in feed "could well be devastating on the large producers."

USDA statistics indicate that there have been some significant changes in pork production. In 1964 the Corn Belt (including Iowa) marketed 49.5 million hogs. Of these, 8.1 percent came from farms producing 1,000 or more animals. At the same time the Southeastern states marketed 9.5 million hogs, 9 percent of them from units of more than 1,000 animals.

By 1974 the Corn Belt's hog marketing had dropped to 43 million, with 23.5 percent from units of more than 1,000 animals.

The Southeast in 1974 marketed 11.3 million hogs, with 34.3 percent from the larger production facilities.

The USDA report states that large hog enterprises play a more dominant role in the Southeast and in the Southwest, and that the rapid increase in the size of pork operations parallels a general trend in farm size, in commodity specialization, and in the adoption of new production technology.

James Nix, a USDA economist, said that antibiotics "certainly" have made possible the larger pork enterprises, and he added: "The larger and larger producers are relentlessly more efficient. As the market turns against them they are still in business, while the smaller, less-efficient producers are squeezed out."

The USDA's Gilliam said that antibiotics in animal feed have been seen as "a substitute for management, an extension of management. Use of drugs has been a substitute of a chemical for hours of oversight."

Statement of

William D. Heffernan and Gary Green

Department of Rural Sociology

University of Missouri - Columbia

before the

House Subcommittee on Interstate and Foreign Commerce

Subcommittee on Health and Environment

We became interested in the issue of antibiotics in feeds when we became invited in the CAST Task Force on "Antibiotics in Animal Feeds." It became obvious at the outset that the antibiotics issue focused on two important societal goals. The first is to provide inexpensive food for consumers and the second goal is the assurance of a healthy population both now and in the future. The proposed legislation raises the questions of whether we can maximize both of these goals simultaneously and what is the possible cost to society by prohibiting or not prohibiting the use of antibiotics in feeds.

Unfortunately a decision must be made before we have complete information concerning the cost and benefits to society of using antibiotics in feeds. Currently, it is relatively impossible to design a research project that would give us "the final answer" concerning the probability of a major negative health impact for society. Likewise, we do not have sufficient information to make a definitive statement concerning the economic and social impact the ban would have on the price of meat for consumers. In the absence of adequate information, economic models are utilized which are based on a host of assumptions. These assumptions include the effectiveness of alternative products or substitutes for those that are banned, the consequences of improved husbandry practices to partially compensate for the use of antibiotics, the consequences the ban will have on the structure of the livestock industry, and the consequences on the efficiency of production. These variables, plus others, will affect the price consumers pay for animal products and the long-term versus the short-term consequences. Various "experts" have made assumptions based on the best information they have, but the input from the farmers who actually produce the animals has been quite limited. We could find no study in which a random sample of farmers was asked what the consequences of prohibiting antibiotics in feeds might be for their farming operation. In no way are we challenging information presented by farm organizations, but studies which have looked at membership in farm organizations indicate that members of farm organizations (and all members of farm organizations tend to be voluntary) do not represent a random sample of farmers. We felt it would be useful to get the farmer's best estimations of his use and the impact prohibiting these drugs would be for their farming operations.

Our purpose is to share with you information we received from farmers. The information will give some insight into the economic and social consequences of restricting antibiotics, but it represents only a small segment of the body of knowledge that is needed to assess the social and economic impact. We do not even attempt to address the health issue. Given our limited scope we cannot take a position on the proposed legislation.

During the summer of 1979 a random sample of farmers from across Missouri was drawn. In August 1979, they were sent a questionnaire, which included questions about their farm operation (such as farm enterprises) and asked them to cooperate in the state farmer opinion poll which would be conducted periodically. A total of 1175 farmers responded. In April of 1980 the same sample of farmers were sent a second questionnaire on which questions concerning antibiotics were included. Only 1054 farmers responded. This analysis is based on the 1051 farmers who responded to both questionnaires. (We appreciate the cooperation of the farmers and Joel Hartman and Paul Lasley who conducted the poll for making this information available to us.)

The data in table 1 indicates that 14% of the farmers reported that they always purchased animal feed with antibiotics, 48% said they sometimes purchased such feed and 24% said they never purchase feed with antibiotics. Fourteen percent of the farmers do not know whether their feed contains antibiotics. When asked about the consequences for their operations if antibiotics were prohibited, 24% of the farmers felt it would have a serious effect on their farming operations, 47% felt it would not have a serious effect on their operation and 29% said prohibiting the use of antibiotics as feed additives would have no effect on their farming operation.

Because many farmers depend little on livestock for farm income and because the consequences of restricting antibiotics as feed additives may have different consequences for different livestock enterprises, we divided the farmers based on whether they said: (1) beef, (2) swine, (3) dairy or (4) poultry products. Their responses to the same two questions were then analyzed.

Data in table 3 suggests that compared to beef, dairy, and poultry producers a higher percent of pork producers always buy feed with antibiotics and higher proportion of the pork producers felt that if the antibiotic additives were prohibited it would have a serious effect on their farming operation. Over a fourth of the pork producers in the State of Missouri reported that they always purchased animal feed with antibiotics, over one-half indicated that they sometimes purchase antibiotics in animal feed. Less than 10% indicated that they never buy animal feed with antibiotics. Percent of total farm sales from hog sales appears to have little relationship to purchasing of feed with antibiotics.

In the case of beef producers 14% of the producers said they always purchased feed containing antibiotics and 58% of them said they sometimes purchased feed containing antibiotics. Eighteen percent of those who obtained less than half of their farm sales from beef sales said they always purchased animal feed with antibiotics while only 11% of those farmers who received over half of their farm income from beef always purchased animal feed with antibiotics. Sixteen percent of the beef producers who obtain over half of their income from beef sales indicated they do not know whether their feed contains antibiotics. A fourth of those who obtain over half of their farm income from beef indicate they never purchased feed with antibiotics.

Thirteen percent of the dairy farmers said they always purchased feed with antibiotics. For those farmers obtaining less than 50% of their farm income from dairying, 8% said they always purchased feed with antibiotics. Fourteen percent of those receiving more than 50% of their farm sales from dairy said they always purchase animal feed with antibiotics. Almost half of the dairy farmers said they sometimes purchase feed with antibiotics and 31% reported they never purchased feed containing antibiotics. One-third of the farmers receiving 50 percent or more of their farm income from dairy products indicated they never purchased animal feed with antibiotics compared to 17% of those who depend upon dairy sales for less than half of their farm sales.

So few poultry producers appeared in our sample it is rather hazardous to draw many conclusions. However, nineteen percent of all poultry producers reported that they always purchased animal feeds with antibiotics, while 19% said that they never purchased animal feeds with antibiotics. For poultry producers with less than 50% of their total sales from poultry, 24% reported they always used animal feeds with antibiotics, while only 10% of those farmers with more than 50% of their sales from poultry said they always purchased animal feeds with antibiotics.

One fourth of the beef producers in the state felt that if antibiotic feeds were prohibited it would have a serious consequence for their farming operation. The data suggest, however, that 30% of the farmers for whom beef production is a minor enterprise (less than 50% of their total sales) felt that prohibiting antibiotics would have a serious consequence for their farming operation. Only 17% of the farmers who received all of their income from beef indicated that prohibiting antibiotics would have a serious consequence for their farming operation. Part of the discrepency between these two categories may result from the farmer considering all his enterprises and not just their beef enterprise. For farmers with most of their income from beef, we can assume they were referring to beef production when discussing the effect for their farming operation. For those farmers receiving less than 50% of their income from beef they may have been thinking of other livestock enterprises such as hogs. The question asked the consequence for their farming operation and not just the beef enterprise.

About a third of the farmers who received less than half of their income from hogs felt that withdrawing antibiotics would have a serious effect on their farming operation and 48% of those farmers receiving 50% or more of their total sales from hogs felt that the withdrawing of antibiotics would have a serious effect on their farming operation. Almost one-fifth of all dairy farmers felt that prohibiting antibiotic feed additives would have a serious effect on their farming operation and about one-third of the poultry producers felt that withdrawing antibotics would have a serious effect for their farming operation.

Those farmers who did not purchase medicated feeds were asked why they did not. Data in table 2 suggest that for all four types of producers the majority indicated that they thought antibiotics did more harm than good. Some felt that they were too expensive and 19% felt that they didn't have any effect. Only a few of the farmers indicated that they were not available. Farmers were also asked if they felt that the use of antibiotic feed additives would reduce effectiveness of these antibiotics for future treatment. Over a third of the farmers indicated they felt that the use of antibiotics on a routine basis would compromise treatment with these antibiotics. Less than a fourth of the farmers said no and the remaining farmers indicated they didn't know.

The general feeling is that antibiotics are more important for large confinement livestock operations than for smaller more dispersed operations. We did not have information concerning the number of livestock units for each farm, but we did have a measure of the gross farm sales. Using just those farmers who reported receiving 50% or more of their farm income from either hogs or beef cattle we divided them into those with gross sales of less than $40,000, $40,000 to $99,999 and more than $100,000 (Table 3). We could not do the same with poultry and dairy producers because not enough of the producers appeared in our sample to legitimately perform the analysis. For pork producers with gross farm sales of less than $40,000, 26% reported that they always purchased animal feeds with antibiotics. Forty-six percent of the farmers with gross farm sales from $40,000 to $100,000 and 26% of hog producers with over a $100,000 gross farm sales reported that they always purchased animal feeds with antibiotics. For those farmers with more than 50% of their farm income from hogs and a gross farm sales of less than $40,000, 36 percent felt that if antibiotics were prohibited it would have a serious consequence for their farming operation. For those farmers with gross farm sales between $40,000 and $100,000, 61% felt that if antibiotic additives were prohibited it would have serious consequences for their farming operation and for the larger hog operations, and for those with gross sales of over $100,000, 74 percent said that the banning of antibiotics would have serious consequence for their farming operation.

Data in table 3 reports results for those Missouri farmers that received over 50% of their farm sales from beef sales. Only 10% of those farmers with gross farm sales of less than $40,000 said they always purchased animal feed with antibiotics while 19% of the beef farmers with gross farm sales of $40,000 to $99,999 indicated they always purchased feed with antibiotics and 23% of the largest beef producers said they always purchased livestock feed containing antibiotics. About 12% of those farmers with gross farm sales less than $40,000 felt that the prohibiting of antibiotics as feed additives would have a serious effect on their farming operation. This compares to 43% of the farmers in the medium size category ($40,000 to $100,000 gross sales) and 50% of those beef farmers who have gross farm sales of over a $100,000.

The results of this study would suggest that the larger livestock operations tend to use antibiotics more often and feel that banning antibiotic additives would have a serious consequence for their farming operation. Another way of looking at size of farming operations is to look at percent of labor provided by hired workers. As farms get larger, the labor available from the farm family becomes less adequate and a higher percent of labor is hired. Data in Table 4 indicate that there is little difference in the use of antibiotics between those farming operations which hire less than 50% of the labor and those that hire workers to provide over half of the labor requirements. There is a rather large difference in the consequences they perceive a ban on antibiotics would have for their operations. Twenty-three percent of the farmers operating units on which less than half of the labor indicated that prohibiting the use of antibiotics would have a serious effect on the farming operation while almost half (45%) of those managers of the farms on which over half of the labor was hired labor indicated that banning of antibiotics would have a serious effect.

SUMMARY

Most livestock producers do use antibiotics in feed. But only about 15 percent said they always buy feed containing antibiotics. An equal number of farmers do not know if their feed contains antibiotics. On the other hand, one-half of the farmers use antibiotics in the feed sometimes. One-fourth of the farmers say they never use antibiotics as feed additives.

Although the majority of the farmers do use antibiotics as feed additives, the majority also said the consequence of banning antibiotics would have little or no effect in their farming operation. Only a fourth of the farmers felt such a restriction would have a serious consequence for their farming operation.

Pork producers, especially large pork producers would experience the greatest impact. But even 30% of the large pork producers said the restriction would not have a serious consequence for their farming operation.

About half of the farmers who never use antibiotics as feed additives said they felt the disadvantage of the feed additive outweighed their advantage. One-third of the farmers feel that the regular use of antibiotics additives in feed rations reduces their effectivenes for future use in treatment. Twenty percent disagreed and half of the farmers didn't know.

TABLE 1

Farmers' Responses to Whether They Purchase Animal Feed With Antibiotics and the Consequence of a Ban on Antibiotics By Enterprise and Per Cent of Farm Income From the Enterprise

	Purchase Animal Feeds With Antibiotics					If Antibiotic Additives Prohibited, Seriousness of Effect for Farming Operation			
	Yes Always	Yes Sometimes	Never	Don't Know	Number of Cases	Serious	Not Serious	No Effect	Number of Cases
All beef producers	14	50	22	14	744	25	47	28	718
Less than 50% of total sales from beef	18	53	19	10	267	38	43	19	260
More than 50% of total sales from beef	11	49	24	16	479	17	49	34	458
All pork producers	27	58	8	7	288	42	44	14	269
Less than 50% of total sales from pork	24	56	10	10	158	35	50	15	149
More than 50% of total sales from pork	32	59	6	3	130	48	41	11	130
All dairy producers	13	47	31	9	68	21	45	34	65
Less than 50 of total sales from dairy	8	75	17	0	12	25	58	17	12
More than 50% of total sales from dairy	14	41	34	11	56	21	41	38	53

TABLE 1 (Cont.)

	Purchase Animal Feeds With Antibiotics					If Antibiotic Additives Prohibited, Seriousness of Effect for Farming Operation			
	Yes Always	Yes Sometimes	Never	Don't Know	Number of Cases	Serious	Not Serious	No Effect	Number Of Cases
All poultry producers	19	51	19	11	25	30	33	37	27
Less than 50% of total sales from poultry	24	29	29	18	17	18	47	35	17
More than 50% of total sales from poultry	10	90	0	0	10	50	10	40	10
All farmers in sample	14	48	24	14	976	24	47	29	934

TABLE 2

Farmers' Responses to Why They Do Not Purchase Medicated Feeds and Whether They Feel Used Antibiotics as Additives Reduces Their Effectiveness for Treatment by Enterprise and Per Cent of Farm Income From Enterprise

	Do Not Purchase Medicated Feeds Because					Use of Antibiotic Additives Reduces Effectiveness For Future Treatment			
	Not Available	Too Expensive	Think They Don't Have Any Effect	More Harm Than Good	Number of Cases	Yes	No	Don't Know	Number of Cases
All beef producers	4	23	19	54	169	37	22	41	730
Less than 50% of total sales from beef	4	24	19	53	47	40	26	34	262
More than 50% of total sales from beef	4	22	22	52	127	36	20	44	468
All hog producers	0	33	13	54	24	34	33	33	282
Less than 50% of total sales from hogs	0	31	19	50	16	35	28	37	153
More than 50% of total sales from hogs	0	50	0	50	10	33	39	28	129
All dairy producers	6	29	18	47	15	39	17	44	66
Less than 50% ot total sales from dairy	0	50	0	50	2	38	8	54	13
More than 50% of total sales from dairy	7	26	20	47	15	40	19	41	53

TABLE 2 (Cont.)

	Do Not Purchase Medicated Feeds Because					Use of Antibiotic Additives Reduces Effectiveness For Future Treatment			
	Not Available	Too Expensive	Think They Don't Have Any Effect	More Harm Than Good	Number of Cases	Yes	No	Don't Know	Number of Cases
All poultry producers	0	33	0	67	6	47	6	47	30
Less than 50% of total sales from poultry	0	33	0	67	6	45	5	50	20
More than 50% of total sales from poultry	0	0	0	0	0	50	10	40	10
All farmers in sample	4	29	19	48	1051	32	20	48	1051

TABLE 3

The Responses of Farmers With 50 Per Cent or More of Their Farm Income From Beef or Pork Sales by Gross Farm Sales

	Purchase Animal Feed					If Antibiotic Additives Were Prohibited, How Seriously Would It Effect Your Operation			
	Yes Always	Yes Sometimes	Never	Don't Know	Number of Cases	Seriously	Not Seriously	No Effect	Number of Cases
Beef producers									
Less than $39,999	10	48	25	17	411	12	51	37	394
$40,000-$99,999	19	51	14	16	43	43	43	15	40
$100,000 and over	23	65	12	0	17	50	44	6	16
Pork producers									
Less than $39,999	26	61	8	5	74	36	45	19	73
$40,000-$99,999	46	51	3	0	35	61	36	3	36
$100,000 and over	26	69	5	0	19	74	26	0	19

Table 4

Farmers' Response to Whether They Purchase Animal Feed with Antibiotics and the Consequences of a Ban on Antibiotics by Percent of Labor Provided by Hired Workers

		Purchase Animal Feeds With Antibiotics					If Antibiotic Additives Prohibited, Seriousness of Effect for Farming Operation			
		Yes Always	Yes Sometimes	Never	Don't Know	Number of Cases	Serious	Not Serious	No Effect	Number of Cases
PERCENT LABOR PROVIDED BY HIRED WORKERS	≤ 50%	14	48	24	14	948	23	47	30	906
	> 50%	15	50	18	17	34	45	39	16	31

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MISSOURI FARM NEWS SERVICE
College of Agriculture and Extension Division—University of Missouri-Columbia
Vol. 69 No. 28 July 9, 1980

July 3, 1980

Dear Editor:

It has been called to our attention that the headline on the story concerned with feeding antibiotics to swine in the July 9, 1980 Missouri Farm News Service does not accurately reflect the contents of the story. The revision at the right provides a more accurate headline.

Cordially,

Dick Lee

Dick Lee, Director
Extension Information

Hog Producers Differ on Effects of Antibiotic Ban

Most Missouri hog producers would come out winners if the proposed ban on antibiotics in livestock feed becomes a fact.

"That's because antibiotics are of most benefit to large scale producers where large numbers of animals are kept in confinement. Disease is more of a problem under these circumstances," said Bill Heffernan, University of Missouri-Columbia rural sociologist.

"Most Missouri hog farms are small to medium, partial confinement operations."

A recent poll conducted by Heffernan and Joel Hartman, another UMC rural sociologist, showed that only 13 percent of those surveyed said they always included low levels of antibiotics in their feeds.

"When we checked the survey results more closely, we found that 80 percent were using antibiotics to some extent. But many more of the small producers felt they could get along without them.

"Of those who said they never used antibiotics in their feed, almost 30 percent said antibiotics were "too expensive"; 19 percent said "we do not think they have any effect"; and 48 percent felt the antibiotics "did more harm than good."

But Heffernan and Hartman figured the key question in the poll went like this:

"If the use of these antibiotics as feed additives was prohibited by law, what would be the effect on your farming operation?"

The response: 21 percent said "serious," 42 percent said "not serious," 26 percent said "no effect" and 11 percent responded "not applicable."

"Over 70 percent of the large producers felt the ban would have a serious effect on their operation. These producers have over $100,000 annual income and earn over half of their farm profits from hogs," said Heffernan.

"The rest of the respondents—which you have to say are more typical of the relatively small hog producer you find in Missouri—really didn't think the ban would have that much effect.

The proposal to prohibit antibiotics in livestock feed, first put forth by the Food and Drug Administration, is currently being considered by a House subcommittee on Interstate and Foreign Commerce and another on Health and Environment.

STATEMENT OF

AMERICAN CYANAMID COMPANY
AGRICULTURAL DIVISION
PRINCETON, N.J.

ANTIBIOTIC PRESERVATION ACT H.R. 7285

Antibiotics have been used in animal feeds for 30 years for growth promotion, improved feed efficiency and disease control. This practice has allowed the development of highly efficient meat production methods where energy, space, time and manpower have been reduced to a cost-efficient minimum. The benefits have been shared by the agricultural industry as well as the consumer. Americans now spend a lower percentage of their income per pound of meat than residents of any other country in the world. Although tetracyclines and penicillin products were originally included in the diet only to improve growth and feed efficiency, it soon became apparent that their use significantly reduced bacterial disease often seen in livestock. Nevertheless, questions concerning the use of feed antibiotics and the development of antibiotic resistance have been studied on numerous occasions for 25 years. These include a 1955 Conference sponsored by the National Academy of Sciences, the Netherthorpe Committee in England in the early 60's and again in the mid-60's, followed by the Swann Committee in 1969; in the United States - the FDA Task Force in 1972, the National Advisory Food and Drug Committee (NAFDC) in the mid-70's, the Office of Technology Assessment report in 1979, the National Academy of Sciences (NAS) report in March 1980 and the yet-to-be-released report of the Council of Agricultural Science and Technology (CAST). A careful study of the science and politics of all these studies leads to certain conclusions.

1. There has been no consensus among respected experts on each committee concerning the reality of a public health threat from feed antibiotics.
2. The evidence to clearly establish the existence or extent of the threat is not available.

The conclusions reached by various committees and individual committee members were often quite different. For example, the Netherthorpe Committee found no need for further restrictions in England, yet the Swann Committee a few years later favored control of certain antimicrobials by veterinary prescription. The FDA Task Force report was issued, accompanied by a memorandum, signed by 7 of the 15 members of the Task Force, which strongly disagreed with some of the statements in the report. In 1976, when the three subcommittee members of the NAFDC issued a report suggesting restrictions on penicillin and tetracyclines, the parent committee, with its wider range of expertise, voted unanimously against the recommendation for restrictions on tetracyclines, saying they were not justified. The recently released NAS report on Human Health Effects of Animal Feed Antibiotics mentions the division of opinions on the committee and the development of the yet-to-be-released CAST report was characterized by acrimony and emotion-laden disagreements.

The lack of reliable scientific information needed to assess the question was pinpointed in the recent NAS report and is reflected in the FDA's program of funded research. Currently, five contracts totaling more than one million dollars deal with this question. They include support for work at the University of Alabama, the University of Missouri, Peter Bent Brigham Hospital in Boston, the Public Health Research Institute of the City of New York, and Colorado State University. In addition to these programs, the FDA is currently considering the design of epidemiological studies of the sort suggested in the NAS report. Funding of 1.5 million dollars has been designated in the FY 1980 Appropriations Bill for such studies. The bill's language has clearly specified that because of the uncertainties involved, no regulatory action should be taken until epidemiological studies or evidentiary hearings are completed.

Several questions raised by the subcommittee on Health and Environment were directed to witnesses at the hearings on June 12 and June 24 and, in some cases, answers were incomplete or inaccurate. The following is meant to provide specific information which the subcommittee sought.

Continued Efficacy of Tetracyclines and Penicillin in Animals

Dr. Virgil Hays of the University of Kentucky presented a comprehensive report as an advisor to the OTA Study Committee. In it, he indicated that the tetracyclines and penicillin products continued to produce marked increases in growth promotion and feed efficiency many years after their introduction. Current university and experiment station studies support that conclusion. Shipping fever, anaplasmosis, liver abscesses, bacterial scours and other endemic microbial infections continue to be controlled by tetracyclines. Careful disease and mortality figures are usually kept by large livestock producers and failure of a particular product would soon become apparent. Monfort of Greeley, Colorado, one of the largest cattle operations in the United States, reports that the decrease in mortality, morbidity and liver abscess condemnations seen initially has been maintained since the introduction of tetracyclines in their feeds many years ago.

Substitutes Available

To discuss substitutes for tetracyclines and penicillin, it is necessary to define whether growth promotion/feed efficiency or disease control are being considered. Most of the substitutes are narrow spectrum, non-absorbed antibiotics which have growth promotion activity but little, if any, activity in preventing systemic bacterial disease in animals. Tetracyclines and penicillin have unique disease control properties not shared by the so-called substitutes. It is not clear from H.R. 7285 which antibiotics would be allowed as substitutes. If all antibiotics used in human medicine and those related to human antibiotics are restricted, only flavomycin will be left for animal use. This antibiotic has no disease control claims at all.

Effect of Restrictions in Europe

The country which first restricted antibiotics in feed was England. The well-known Swann regulations were imposed in 1971. Recently, a clear acknowledgment of the failure of their restrictions has appeared. (*British Medical Journal* - May 17, 1980, *Veterinary Record* - June 7, 1980.

Antibiotic resistance in animal *E. coli* and salmonella has not been reduced in England, but has increased in most cases. Even if a reduction in such resistance had been accomplished in animals, it is highly doubtful that a concomitant improvement in antibiotic efficacy in humans would have been seen. The suggestion that a reduction in antibiotic resistance in certain salmonella strains in Germany and the Netherlands has been a result of restrictions is without foundation. Resistance in salmonella often rises and falls depending on strain predominance in a given location. Cherubin has recently reported on a marked reduction in salmonella resistance in New York City in the last several years. (J.A.M.A. 243:439, 1980) Obviously, no new Federal regulations can account for it.

Antibiotics Currently Retained for Human Use

There are antibiotics used extensively in human medicine that are not used in animal feeds. They include gentamicin, kanamycin and several other aminoglycosides, all of the cephalosporins, the semisynthetic penicillins, and chloramphenicol. Antibiotic resistance to some of these is currently increasing in humans, but not in animals in the United States. Chloramphenicol resistance in bacterial isolates from livestock is much rarer in the United States than in Europe and reflects the relatively widespread use

of this product therapeutically overseas. Its use in meat animals in the United States is illegal.

Transfer of Animal Bacteria to Humans

Since cooking destroys bacteria, how is the consumption of meat regarded as a potential source of antibiotic resistance? On the occasions that humans consume animal bacteria, a breakdown in hygienic measures has taken place. For example, the level of bacterial contamination on meat reflects the hygienic and storage history from slaughterhouse to consumer. Then the mechanism of dissemination in the home also reflects kitchen hygiene, the use of contaminated knives, utensils, cutting boards, etc. The most common cause of food borne disease is failure to refrigerate food that has inadvertently become contaminated. It is not likely that these bacteria could survive the high temperatures of broiling, baking, boiling or frying. It should be emphasized that experiments have shown that E. coli from animals usually fail to establish themselves in the human gut, even when ingested in very high numbers.

The Antibiotic Preservation Act (H.R. 7285) and its introductory preamble presents inaccurate information as well as statements based on uninformed speculation. This misinformation was referred to by Congressman Rose, Congressman Carter, Dr. Hewitt, Dr. Stallones and Dr. Finkel during the June 12 hearing. The bill is based on several false assumptions.

1. ***Antibiotic resistance in bacteria has rendered some antibiotics useless in the therapy of human infectious disease and the continued efficacy of all antibiotics is threatened.***

   This is not true. The extent of antibiotic resistance in clinical medicine is grossly exaggerated in the bill and in its preamble.

There is no reason to believe that resistant pathogens will eventually predominate and that alternative therapy will be unavailable.

2. *The use of human antibiotics at subtherapeutic doses in animals is a major (or* *__the__* *major) cause of this situation.*

   This premise is also untenable. It's unlikely that any infectious disease expert would support this premise. Even the most ardent opponents of feed antibiotics in livestock agree that use of antibiotics in humans is the primary cause of antibiotic resistance in humans.

3. *These antibiotics (penicillin, tetracyclines) are used for growth promotion and effective substitutes exist which are not used in humans.*

   Tetracyclines and penicillin promote growth and feed efficiency, but are used primarily for disease prevention. No effective substitutes exist for many of the diseases controlled by these products. Although other growth promoting antibiotics exist, they are often more expensive and less effective than the tetracycline products.

4. *If "Human" antibiotics are no longer permitted for growth promotion, their effectiveness in humans will be preserved.*

   This is an illogical assumption. If __subtherapeutic__ antibiotics are restricted, the need for __therapeutic__ antibiotics in livestock will increase, so it is unlikely that antibiotic resistance in the bacteria of __animals__ will be reduced. Also, since antibiotic use in __humans__ would be unchanged, there is no reason to believe that restrictions could help preserve their effectiveness.

Several of the examples cited in support of the bill require detailed comment. The bill states that the continuous use of antibiotics in subtherapeutic amounts has resulted in the development of pathogenic bacteria in animals that are resistant to these and other antibiotics. There is no evidence that this is true. The recent NAS report clearly points to the difficulty of separating the effects of therapeutic and subtherapeutic antibiotic use as a source of resistance. The bill further states that such pathogenic bacteria in animals are transmitted to humans where they cause diseases (such as meningitis, gonorrhea, and salmonellosis) for which there is virtually no effective antibiotic treatment. Neither meningitis (Haemophilus influenzae) nor gonorrhea is derived from animals and there is no evidence that their resistance was derived from animals. It is also untrue that there is no effective treatment for these human diseases. Salmonellosis can result from consumption of contaminated food, but usually is a self-limiting enteric disease in which antibiotics are not used. Effective antibiotics are available for the less frequent systemic infections.

Congressman Dingell's examples of antibiotic resistance in humans are somewhat misleading, are often exaggerations and are not relevant to animal feed antibiotics. For example:

"Penicillin, once the drug of choice for treatment of H. influenza..... is now virtually useless for such therapy and has been supplanted by chloramphenicol."

This organism is not zoonotic and not derived from animals. The isolation of beta-lactamase producing strains of this organism and the genes coding for this property are unlikely to have come from an animal source. A recent national survey of antibiotic sensitivity of this organism indicates that more than 95% of the isolates are susceptible to the beta-lactam antibiotics (penicillin, ampicillin, etc.) so to say that they are "now virtually useless" is a gross exaggeration.

"Tetracycline highly effective in treating the life-threatening disease of cholera until recently is now a futile regimen."

Cholera is a disease caused by Vibrio cholerae, an organism which is not found in meat animals. Further, the disease is very rarely found in the United States and no possible influence of feed antibiotics can be postulated. In those parts of the world where cholera is sometimes a problem, patients are treated by restoring fluids and electrolytes. Antibiotics are of limited usefulness and then only at early stages of the disease. The major method of controlling cholera is by improving sanitation and preventing the contamination of water and food by human excrement.

"Ampicillin - a semisynthetic penicillin was virtually 100% effective against the virulent human pathogen, salmonella in 1967, now only one in four salmonella infections is effectively treated with ampicillin."

Ampicillin was first used in humans in the early 60's and ampicillin resistance was first seen in human salmonella isolates. It was not until therapeutic use in animals was approved in the early 70's that resistant salmonella was seen in animals. This argues against the idea that two decades of penicillin use in animals had any effect on ampicillin resistance. Therapeutic use of ampicillin in man and animals is the primary cause of ampicillin resistance in salmonella. Cherubin has reported a sharp decrease in ampicillin resistance in S. typhimurium isolated in New York City patients since 1975. (J.A.M.A. 243:349, 1980)

Meyer has reported significant decreases in ampicillin resistance in Shigella isolated in the Midwest. (Antimicr. Ag. and Chem. 17:101, 1980) There is no convincing evidence that ampicillin resistance in humans is influenced by subtherapeutic use of antibiotics in meat animals.

"Also, 85% of all enteropathogenic E. coli, one of the most common causes of human dysentery, have been shown to be completely or partially resistant to nine of the most common human therapeutic antibiotics."

This may be true but since human enteropathogenic E. coli have never been shown to come from animals, is not relevant to the subtherapeutic use of antibiotics in meat production. Furthermore, E. coli gastroenteritis in humans is not usually responsive to antibiotic treatment, whether or not the organism is antibiotic resistant.

Congressman Dingell's statement concerning the NAS report was particularly misleading. He said *"the report concludes that the research necessary to quantitatively measure the human health risks could not be realized, etc."* The report in truth says *".....a comprehensive, all-encompassing study could not be realized or even approximated because of insurmountable technical difficulties."* (Emphasis added.) The distinction is important since the NAS Committee did recommend four types of studies.

The report described the technical difficulties of separating the effects of therapeutic and subtherapeutic uses of antibiotics in animals. The report further says, *"The committee RECOMMENDS that the future epidemiological studies, whether the ones suggested here or others, be carefully planned to fill gaps in our present knowledge and, especially, to avoid the errors of ambiguous design and small sample size that have caused such difficulties in interpreting the data. The proportionate contributions to resistance made by subtherapeutic and therapeutic uses of antimicrobials in animals and in humans urgently need resolution."*

Congressman Dingell referred to a recent paper in JAMA as follows. *"Skeptical voices are further muted by evidence which appeared in the February 8, 1980 Journal of the American Medical Association verifying the spread of a drug-resistant salmonella infection in animals whose feed-contained antibiotics in subtherapeutic doses, to a hospitalized human population."* Actually, the subtherapeutic antibiotic used was bacitracin, an antibiotic which does not select resistant organisms and presumably is one of the "safe substitutes" mentioned by the FDA. The calves received subtherapeutic tetracycline several weeks after the reported hospital incident.

Antibiotics such as penicillin, ampicillin and the tetracyclines are used extensively in hospitals and by "outpatients." A recent analysis of antibiotic resistance in animals and man led Drs. Richmond and Linton to conclude *".....we must look to the medical, as opposed to the veterinary, use of tetracycline as the main selective pressure for the high incidence of tetracycline-resistant organisms in the human population, and the source of such organisms in human beings not receiving antibiotics is more likely to lie in human beings who are being treated than in the farm animal population."* (J. Antimicr. Chemother. 6:33, 1980) These internationally respected scientists, experts in R-factor epidemiology, have thus reached a conclusion completely different from the one expressed in the bill which is *"......a situation has evolved where the therapeutic value of human antibiotics has been severely compromised or perhaps lost in the name of growth promotion."*

Certainly, we cannot disagree that antibiotic resistance in some pathogens is often a serious impediment to the successful treatment of human disease, particularly where therepy must be initiated before antibiotic sensitivity tests are carried out. Nevertheless, the overwhelming evidence suggests that the increasing use of antibiotics in humans has brought about this situation and that Federal regulations controlling animal feed antibiotics could not aid in the preservation of antibiotic efficacy in humans. We further believe that the existing statutes are sufficient authority for control of these animal health products and that the procedures already initiated by FDA leading to evidentiary hearings are appropriate for the consideration of so complex and controversial an issue. Certainly, where the evidence for a risk to public health is lacking and the potential economic consequences so large, then the evidentiary hearing process is a mechanism suitable for an examination of the many facets of this question. The subject is a difficult one, far more complex than the public health issues normally faced by regulatory agencies and by Congress.

Summary of Fundamental Concerns about H.R. 7285

- FDA stated in recent hearings on H.R. 7285, "*The Agency has in the past and continues to have sufficient authority to take action against products such as these that pose a hazard to human health. Over the past several years, we have been proceeding to implement this authority.*" Were there an imminent danger to human health, FDA could act immediately to restrict these products. There obviously is no imminent danger. Thus, time exists in which to carefully review these complex scientific issues in the proper forum - formal evidentiary hearings. H.R. 7285 would circumvent this important procedure, which Congress has repeatedly stressed.

- A Notice of Opportunity for Hearing was issued by the FDA. Antibiotic sponsors responded by requesting a hearing based on many carefully supported issues of fact. The FDA disclosed that there were indeed issues to be decided and that hearings would be held,

- In addition to the numerous inaccuracies appearing in the bill and its preamble, the bill's purpose is to insure the continued efficacy of human antibiotics. As established in the hearing record if subtherapeutic antibiotics were restricted, therapeutic uses in animals and acknowledged overprescribing in humans would still exist. The bill simply will not accomplish its purpose!

- The issue of subtherapeutic use of antibiotics in animal feed has not been ignored either by Congress or the scientific community. The process to decide on the need for further regulations is proceeding rationally. The National Academy of Sciences was asked to identify where data gaps exist and to recommend appropriate studies to fill these gaps. The NAS recently recommended four such studies. Congress has funded them and added that final action on the issue should not take place before the studies are complete and evidentiary hearings held.

- The threat to human health from use of subtherapeutic antibiotics in animals is theoretical. Its existance has been neither proven nor disproven. If products can be restricted on that basis, a dangerous regulatory precedent will be established.

Because the bill will not accomplish its purpose; because the assumptions on which the bill is based are seriously flawed; because FDA has the necessary authority to protect public health from any danger implied by these products; and because the process to decide the issue is being implemented, we oppose H.R. 7285.

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July 8, 1980

The Honorable Henry A. Waxman
Chairman
Subcommittee on Health and Environment
House Committee on Interstate and
Foreign Commerce
512 Annex 1
House Office Building
Washington, D.C. 20515

Re: H.R. 7285 Introduced to amend the Federal Food, Drug and Cosmetic Act to limit the antibiotic drugs which may be used in subtherapeutic doses in animal feed

STATEMENT OF DR. A. KARIM AHMED AND CHRISTOPHER COLEY OF THE NATURAL RESOURCES DEFENSE COUNCIL

Written for the Record

Dear Congressman Waxman:

The Natural Resources Defense Council (NRDC) is a national not-for-profit environmental organization supported by 45,000 members throughout the country. In keeping with their overriding concern for the status of the environment and the quality of human health, scientists at NRDC have monitored the issue of antibiotic usage in livestock feed for a number of years.

Substantive action is long overdue; indeed, it is difficult to understand or, more exactly, accept the fact that the United States continues to lag behind most of Western Europe and Japan on an issue which poses such a significant, progressive risk to the health of all Americans, with no justifiable compensating benefit. Over the course of several different Congressional Hearings held in 1977, ample evidence was presented, by objective authorities in the fields of microbiology and infectious disease, to support FDA's proposed actions (42 Federal Register 43770). That such minimal steps were not taken speaks more for the influence of the commercial lobbies than for the desire to resolve scientific divisions over this issue.

We are extremely concerned that the recent report* released by the National Academy of Sciences (NAS) may promote a false sense of confidence that the non-therapeutic use of antibiotics in animals poses little, if any, hazard to people. This report simply corroborated what Drs. Stanley Falkow, Richard Novick, Donald Kennedy, and others asserted during the 1977 Congressional Hearings, that there are no data from which to predict quantitatively the change in morbidity and mortality of humans that might result from an increased prevalence of antibiotic-resistant bacteria in animals or from the transfer of these organisms to humans. However, just because it is impossible to measure the contribution of this practice to the problem of antibiotic resistance and the degree of human disease does not relieve government of its responsibility to minimize the risks to the public health. No one will contend that the bulk of our resistance dilemma lies with the nontherapeutic use of these drugs in livestock feed. Modern medicine has undoubtedly contributed inordinately to the problem. However, the crucial point to recognize is that total antibiotic usage selects for a pool of genetic elements, resistance genes on mobile plasmids, that are common and available to an ever-growing list of bacterial species. Antibiotic-resistant bacteria are now so extensively distributed in the general environment that it is sometimes impossible to trace definitively their appearance to a particular usage. Nevertheless we join with those who aver that any unnecessary practice that vitiates the efficacy of the physician's therapeutic armamentarium should be eliminated. As Dr. Joyce Lashof of the Office of Technology Assessment (OTA) stated succinctly, "In policy terms, it is not helpful, only distracting, to point to a potentially larger contributor (like human medicine) to the problem to determine what should be done."* Logic and prudence, based on a sound understanding of the weight of available scientific knowledge, must henceforth hold sway. Merely because the human use of these agents gives rise to a large fraction of the resistant organisms does not proscribe one from preventing another source of resistant strains from entering the "commons."

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*"The Effects on Human Health of Subtherapeutic Use of Antimicrobials in Animal Feeds " (1980).

It is beyond dispute that feeding animals antibiotics on a regular basis greatly enlarges the reservoir of antibiotic resistance genes and multiple-resistance combinations. As those objective scientists, with a comprehensive understanding of the ineluctable workings of plasmid biology, have described in elaborate detail at past Congressional Hearings, the expanding reservoir is a very real, if not quantifiable, hazard. Moreover, as Dr. Tom O'Brien, Director of the Microbiology Laboratory of the Peter Bent Brigham Hospital, so carefully adduced, the larger the pool of resistant organisms, the higher the probability of deleterious consequences. Clearly there are two concentrated preserves of resistance genes within the entire U.S. "commons." One is within our hospitals; the other is the prodigious reservoir induced in our herds and flocks by feeding livestock subtherapeutic levels of antibiotics for the promotion of growth and the prevention of disease. We should like at the outset, however, to register our dissatisfaction with the term "subtherapeutic." The distinction made between so-called "subtherapeutic" and "therapeutic" doses of antibiotics is artificial; the critical difference lies in continuous use, seen with the typical growth-promotion regimen, versus intermittent use, characteristic of the genuine treatment of overt clinical disease.

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*Joyce Lashof, M.D., personal testimony delivered before the House Subcommittee on Health and Environment, June 12, 1980.

It would be foolish to imagine the problems associated with R-plasmids can be eliminated by enacting a single piece of legislation. We also view with skepticism attempts to place the blame for the resistance problem squarely on the shoulders of any one party. Certainly all have a share in the responsibility. Yet even if antibiotic usage in livestock feeds was discontinued immediately, the reservoir of drug resistance in food-producing animals would not soon disappear. Nevertheless we believe the situation may be ameliorated by the general adoption of the prudent and discriminating attitude toward antibiotic usage set forth in the British Government Joint Committee (Swann Committee) report* and the original FDA task force recommendations. The fact that the limited regulations promulgated following the Swann report recommendations have failed to reduce the level of antibiotic resistance in Britain should not be seen as a vindication of the position that regulations in this area are futile. On the contrary, a recent editorial* in the British Medical Journal concluded that the "present state of affairs is unsatisfactory and dangerous and more stringent regulations are needed." We harbor no illusions that legislation alone will rectify the damage already done by excessive use of these drugs in the United States. The problem will have to be dealt with at many levels, including educating farmers and veterinarians as to the potential dangers to both human and animal health by continuous antibiotic usage, as well as meticulous monitoring to insure that the prescription process is respected.

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*"On the Use of Antibiotics in Animal Husbandry and Veterinary Medicine" (1969); referred to today as the Swann report.

There are bound to be many hurdles impeding the effective implementation of the FDA proposed actions. Moreover, we consider FDA's current plans flawed in that among the list of proposed substitutes are certain important human antibiotics, such as erythromycin, and some animal antibiotics (tylosin, virginiamycin) that select for strains of bacteria resistant to erythromycin. Nevertheless, at a minimum, the FDA proposal would cut down the really irresponsible use of antibiotics by the farmers themselves in treating their own livestock, and so begin to establish a system that hopefully will, in the long run, result in substantial diminution of the animal contribution to the resistant gene pool.

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*British Medical Journal, Vol. 280, pp. 1195-1196 (May 17, 1980).

Why It Is Imperative That Congress Pass H.R.7285:

In a statement presented before your Subcommittee on June 12, 1980, the representative of the Animal Health Institute (AHI) offered the opinion that FDA "currently possesses fully adequate authority to deal scientifically and administratively with the issues addressed in the proposed legislation." He went on to say that enactment of this bill would represent "unnecessary Congressional intervention" and would be inappropriate at this time because FDA has initiated proceedings and Congressional Appropriations Committees have directed that additional research be conducted before FDA takes final action. Simply stated, these claims serve merely to obfuscate the critical issue, which has been raised yet again by H.R. 7285.

We have devoted considerable time and effort examining the merits of both sides of this policy question and, from a good comprehension of the science involved, have concluded that the American public cannot afford to wait another six or seven years for the completion of the large-scale epidemiological studies that have been requested in the Appropriations language. All of the necessary scientific data to justify the FDA proposals to restrict the use of antibiotics in livestock feed has been amassed for some time now. Given that the NAS report inferred that it is not possible to conduct a feasible, exhaustive epidemiological investigation to answer the central question that body was charged to consider, that is, to prove definitively the causal chain, we believe Congress should acknowledge the overwhelming scientific information and logic supporting such restrictions.

The majority of every scientific body that has examined this issue in depth has chosen to regard the inexorable increase in the genetic pool of drug-resistant bacteria as the essential yardstick for determining what constitutes a serious risk to public health. As Dr. Lashof stated so cogently, this choice is consistent with the predictive value of science in helping to fashion public policy. We are alarmed by the pervasiveness of the premise that one must first produce the bodies, as it were, before regulatory action will be deemed appropriate. Even today the pharmaceutical industry spokesmen and livestock producers continue to announce repeatedly that in over 30 years of use in animal feed antibiotics have not been directly linked to disease in humans. This type of proclamation reflects a profound misunderstanding of the process of risk-assessment and preventive medicine. Direct evidence of human disease confirms experimental and uncontrolled statistical evidence.

Yet public policy in regulating risks to human health has not relied on controlled epidemiological studies for the primary evidence of risk. It has been repeatedly and conclusively demonstrated that feeding of antibiotics at various dosage levels causes a dramatic increase in the prevalence of antibiotic-resistant bacteria in farm animals, in their products, in their environment, and in people in close contact with these animals.

No one expects bacteria that are simply resistant to antibiotics to cause more infections than those that are not. However, as we will mention later, there is mounting documentation that for certain microbial systems antibiotic feeding may lead to enhancement of pathogenicity, that is, heightened ability to cause disease. The principal danger posed by resistant bacteria, however, lies in the indisputable fact that once you have an infection, it is either more difficult or impossible to treat if the causative agent is refractory to chemotherapy. Based on the impressive corpus of experimental corroboration, it is encumbent upon the members of Congress to enact this legislation. Such an action will provide much needed facilitation of the kinds of restrictions imposed by much of Europe over six years ago.

We concur with Dr. Donald Kennedy's admonition that the imminent hazard procedure must be employed sparingly, for only the most immediate and serious of cases. However, the dangers to human and animal health created by unrestricted non-therapeutic dispensing of antibiotics to livestock warrants special Congressional attention. Given the gravity of the situation and the extensive hearings that have been held on this issue, we adamantly oppose further appropriations for additional long-range studies. There has already been unacceptable procrastination at both the administrative and at the legislative levels. Requests for such protracted data collection will serve only to increase the likelihood that serious harm will be experienced during the many years required in any realistic projection of the administrative process.

As we interpret the spirit of H.R. 7285, passage will confer upon the FDA explicit authority to implement their proposed actions in an expedient manner. This would avoid the certainty of lengthy legal delays and tortuous evidentiary hearings, to say nothing of the time necessary to complete what we deem unwarranted additional studies.

H.R. 7285 is an important piece of legislation. While several of its provisions, 2(2) and 2(3), reflect misunderstandings of the mode by which resistance is transfered and promoted, these errors are of minor importance. They do not detract from the rationale of this measure, which reflects a sound appraisal of the weight of fifteen-odd years of unbiased scientific scrutiny. Our few criticisms of the opening provisions of this bill will be elaborated later in these comments and we offer suggestions to remedy these weaknesses.

In the meantime, we take issue with the comments made by Dr. William Hewitt, who appeared at the June 12 hearing at the request of the Animal Health Institute (AHI). Of course resistance genes have been around for eons; certainly the antibiotics themselves have no magical power of creation. It is a proven fact that oral administration of antibiotics in subtherapeutic and therapeutic doses alike increases the fraction of multi-resistant nonpathogenic and pathogenic bacteria in both animals and man. This is beyond dispute. R-plasmids, though primarily found in intestinal bacteria (the gram-negative enterics to be exact), may be readily transfered from its host to other unrelated bacterial species, some of which are extremely important as pathogens for humans, for example, salmonella - the cause of gastroenteritis, septicemia, and typhoid fever in man - Neisseria gonorrea, the cause of gonorrhea in man; Hemophilus influena b, the primary cause of bacterial meningitis in patients under 5 years of age; Chlamydia psittacii, the cause of psittacosis in animals and man (can present as a severe and sometimes fatal pneumonia-like condition).

Dr. Arthur Saz, Chairman of the Department of Microbiology at Georgetown University Medical School, stressed in the 1977 hearings that there are at least 19 genera and more numerous species of organisms which can go - and have been shown to go - from animals to humans. The ability of disease-carrying organisms to be transmitted from animals to man is not limited, as Dr. Hewitt and Dr. Ascher Finkel imply, to a handful of species, like the salmonellae varieties. Dr. Hewitt is correct in asserting that Section 2(3) of your proposed legislation is technically incorrect. Those pathogenic organisms responsible for causing human bacterial meningitis and gonorrhea do live only in certain human biota, and therefore cannot be transmitted from animals or surrounding environments. It is true, however, that these organisms have very recently acquired the resistance genes, situated on a R-plasmid, from a common inhabitant (E.coli) of the normal gut flora of both humans and farm animals. This has been unequivocally demonstrated by sophisticated biological techniques such as plasmid DMA homology studies and "finger-print" mapping. Possession of these resistance determinants of course compromises treatment and may indeed be life-threatening. For the two examples just mentioned, the evidence strongly suggests that the process of resistance transfer evolved through the application of antibiotics to human conditions. In the case of penicillin-resistant gonococcus organisms, it was sustained flagrant abuse of the drug that ultimately provided the requisite degree of selective pressure to insure the successful transfer of the R-plasmid from a resistant E.coli. Nevertheless, the literature is replete with data to support the thesis that the process of proliferating resistance is equivalent at both the human and the animal levels. The evidence that antibiotic-resistant bacteria in animals can be transfered to human beings is strong. Moreover, this event can occur through a nonpathogenic intermediate, although as Dr. Dwayne Savage notes, the question of whether or not antibiotics tend to increase the relative proportions and absolute numbers of potential pathogens is moot since it has been clearly established that "pathogen" is difficult to define with reference to the human biological niches. Many of the indigenous anaerobic* bacterial species previously considered innocuous are now known to have the capacity to cause disease under the right circumstances. Anaerobic organisms are normally present in the human and animal gut at roughly a ratio of 1000:1 compared to the facultative** bacterial species.

Until recently the anaerobic Bacteroides species, the most common inhabitants of the human colon, were rarely implicated as causative agents of human disease. Today, however, physicians claim these organisms are involved in a significant number of serious clinical conditions, such as septicemia (blood poisoning, 30% mortality) and wound infection (Nature Vol. 274: 113-114, July 13, 1978). A number of recent reports describe the acquisition of a self-transmissible R-plasmid in *Bacteroides fragilis*, the principal villian in infections due to anaerobic bacteria. This species is relatively resistant to a number of antibiotics and thus when encountered clinically poses significant problems for successful chemotherapy. As the Nature article warns, "the presence of conjugative R-plasmids in this genus must inevitably hasten the wholesale acquisition of resistance to these (beta-lactams, e.g. penicillins and cephalosporins) and other antibiotics." It is unclear whether Bacteroides R-plasmids originate within this genus or whether they have been transfered from other bacteria. Furthermore it is impossible to attribute the proliferation of this plasmid to either human or animal use. As aforementioned, this obsession is counterproductive. Antibiotics, wherever and however they are utilized contribute to a common "pool" of resistance. The emergence of transferable drug resistance in Bacteroides is yet another example of bacterial populations responding to the selective pressure imposed by widespread use of antibiotics. In addition to compounding the clinical problems associated with treating conditions caused by these anaerobic organisms, as major constituents of the normal human and animal gut flora, Bacteroides harboring resistance genes also provide a potential threat to human health if they transmit these determinants to more convention pathogens.

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* Survival dependent on the absence of oxygen.
** Able to tolerate both presence and absence of oxygen.

Dr. Hewitt's additional criticims of the provisions of H.R. 7285 are on the whole superficial and serve only to deflect examination of the essential policy question now in the hands of the Congress. We agree that Section 2(4) is vague and adds little strength to the raison d'etre of this legislation; it could easily be deleted. However, the OTA report, like those of similarly constituted bodies before it (Swann report, FDA Task Force, WHO) clearly delineated the "increasing pool of resistant bacteria" as a serious human health risk. We do not find this at all "arbitrary." This choice is based on a sound appraisal of the copious scientific studies which demonstrate the significant part played by chronic antibiotic usage in livestock feed practices in expanding the genetic pool of resistance bacteria. The differentiation between so-called "animal" and "human" strains of coliform and many other bacteria is fading. The organisms in animals may contribute their R-plasmid to man by several different, though obviously related mechanisms, for example, by direct contact of humans with animals harboring resistance microbes; by contact of humans with foods contaminated by resistant organisms; by contact of humans with environment contaminated by resistant bacteria.

Dr. Hewitt implies that because an unequivocal reduction in drug-resistance has not been forthcoming in Western Europe, restrictions are futile or even counterproductive. We disagree wholeheartedly with this type of thinking. Just because the mechanisms for implementing the original recommendations have experienced impediments is hardly reason to discredit the rationale behind them. Retrospective analysis carried out in the United Kingdom to ascertain why their regulations have not produced the expected benefits has elucidated a spectrum of contributing factors. An apparently significant resistance problem has evolved through the use of such antimicrobials as chloramphenicol and trimethoprim, both of which are unapproved for animal use in this country, although they are undoubtedly utilized by some American farmer on a clandestine basis.

Veterinarians who are unconvinced or unaware of the hazards posed by the indiscriminate nontherapeutic use of these drugs in farm animals figure into the equation of regulatory failure in Britain. There is substantial evidence that the therapeutic usage, that is via the veterinary prescription, grew to such an extent that the overall volume of antibiotics utilized for animals changed little. Moreover, drug company representatives and black market operators may be finding farmers "all too ready to sidetrack their veterinarians and to bid for any supplies of prescription-only antibiotics that may become available through irregular channels (British Medical Journal Vol. 280, p. 1195-6, May 17, 1980). Lastly, the continued uncritical prescribing of antibiotics by the medical profession was also cited as contributing to the continued unacceptably high levels of antibiotic resistance. However, far from throwing up their hands in despair, the editors of this prestigious medical journal laid down the challenge to ameliorate the situation, proclaiming that all parties concerned must become more assiduous in their behaviour; more "stringent regulations," they conclude, are the order of the day.

The situation in the Netherlands, where restrictions similar to those proposed by the FDA have been in effect since 1974, is one of mixed success, although there is an obvious paucity of data from which to judge. van Leeuwen _et al_ report* that subsequent to 1974 tetracycline resistance in salmonellae of human and pig origin has diminished nationwide; this decline has coincided with a ban on the incorporation of tetracyclines into animal feeds. Interpretaion of this drop is made difficult by the apparent significance of a specific type (505) of the species _Salmonella_ _typhimurium_, the most common member of this family plaguing man and pig. A decrease in the prevalence of type 505 parallels the diminution of tetracycline resistance in all salmonellae. But it is hard to discern whether this change was due to the restrictions on growth promotion usage of the drug, imposed in 1974, or to a natural cyclical fluctuation in virulence. The authors seem to ascribe the decline in resistance to the restrictions and not merely to an artifact imposed by natural variation of this one bacteria type, but there is room for disagreement. It should be noted, however, that by far the sharpest drop in the tetracycline-resistance type 505 strain im both man and pig came during the year immediately following the enactment of restrictions.

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* _Antimicrobial Agents and Chemotherapy_ Vol. 16, No. 2, p. 237-239, August 1979

Scientists do not know, nor have no accurate method of predicting, precisely how much time after the implementation of the FDA proposed regulations, assuming all parties adhered to them as anticipated, would be required before one could detect a noticeable decline in drug-resistance. In all likelihood, it would be a matter of some years, but it is imperative that efforts begin now to halt the progressive increase in the environmental pool. According to the 1976 WHO panel of international experts that investigated the issue, "this (environmental) pool will continue to increase in size even in the absence of antibiotics, but its enlargement will rise more steeply in their presence, because of the strong selection pressure they exercise."

In a study sponsered by the Animal Health Institue (AHI), comparisons were made between a Coldstream swine herd fed chlortetracycline (CTC) continuously since 1972 and a herd at Princeton, which had not received antibiotics therapeutically or in feed since 1972. The researchers discovered that in the 3 years following the removal of CTC from the Princeton herd, tetracycline resistance averaged approximately 40 percent, while remaining almost 85 percent in the Coldstream herd still being given antibiotics. One would not witness such a precipitous fall-off following enactment of H.R. 7285, even if one could guarantee the cessation of all non-therapeutic usages of tetracycline in chronic animal feeding. But this study is valuable for demonstrating that under stringent conditions the resistance problem is, to a limit reversible.

Therapeutic usage, as it is defined in the veterinary sense of short-term high-dose treatment of overt disease, would produce resistance bacteria just as it does in human medicine. However, the essential distinction, as aforementioned, is not high-dose vs. low-dose, but rather indiscriminate and continuous usage throughout the life of the animal vs. the intermittent and prudent usage by a qualified veterinarian. It has been shown conclusively that the continuous administration of these drugs is more likely to promote plasmid carriage than highly selective use, i.e., when one is confronting clinically manifest illness.*

Enactment of H.R. 7285 followed by rigorous and comprehensive implementation would provide a salutory curb on the proliferating problem of resistance in the U.S. and the world, by reducing the vast quanitity of resistant microbes produced in American feedlots, a system Dr. Tom O'Brien has likened to a "vast recombinant DNA laboratory."*

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* Linton _et al_, _J_. _Appl_. _Bacteriology_ 38: 255-275 (1975)

As with the animal studies cited earlier, it has been documented that through an assiduous attempt to minimize the unnecessary use of antibiotics a hospital can drastically reduce the prevalence of resistant organisms in situ. We will never eliminate the debilities in therapy created by R-plasmids, but it is vital to the future visibility of American medicine that this problem be addressed on all fronts. Any unnecessary or marginally beneficial practice that contributes to the ineffectiveness of antibiotics for the treatment of human and animal disease should be disallowed. Even if one were able to ignore all the negative aspects, close scrutiny of the data proffered in support of the non-therapeutic use of antibiotics in animal feed reveals little to recommend continued sanction of this practice. The putative benefits are highly suspect given the paucity and poor quality of existing studies. With regard to the issue of efficacy of this practice, we find it significant that:

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* O'Brien NAS Report, "The Effects on Human Health of Subtherapeutic Use of Antimicrobials in Animal Food," Appendix I. In using the analogy of a recombinant DNA laboratory, by definition a wholly human phenomenon, Dr. O'Brien hoped to illustrate that exposing the bacterial flora component of animals to continous loads of antibiotics represents an ideal opportunity for the evolution of efficient antibiotic resistance mechanisms. It should be clearly understood that just as there are many types of antibiotics, with different modes of action, there as many ways bacteria can become resistant to chemotherapy. More importantly, if there are qualitative differences between resistance mechanisms, the influence of resistance in one animal's bacterial flora compartment on that of another may be completely out of proportion to the rate of exchange between them. In other words, if a particular mechanism is qualitatively so "fit" for a certain bacterial flora, then once it is introduced into that bacterial compartment it circulates widely. O'Brien asserts that current practices in the feedlot, where there is recycling of large numbers of the same strains of bacteria through successive rounds of exposure to antibiotics, would seem to favor reassociation of antibiotic resistance genes and other genes toward the development of more efficient resistant mechanisms and more efficient distribution. Simply stated, this use of antibiotics greatly improves the likelihood of generating qualitatively different resistant organisms with better "fitness."

(1) there has yet to be submitted data that elucidates the effectiveness of antibiotics for growth promotant purposes in the absence of disease prevention. No detailed mechanism for these purported effects has been forthcoming.

(2) there is no parallel in human medicine, where giving a "subtherapeutic" dose of 18 or so different antibiotics will cause a population to be healthier. It is curious indeed that 18 different chemotherapeutic agents, all presumably acting with a different mechanism, would be capable of improving the health of animals.

Moreover, as Dr. Saz testified at the 1977 hearings, some of the antibiotics which supposedly are helping prevent liver abscess have absolutely no effect upon the organism which is presumably causing them (Hearings before the Subcommittee on Agricultural Research and General Legislation, September 21 and 22, 1977, p. 77).

(3) in a recent edition of Feedstuff (2/18/80), a farmer's trade journal, one finds two important papers written by animal health scientists with obviously a critical eye. Dr. Jim Green, of the Missouri Farmers Association, asks whether the hog industry has reached a point similar to the poultry industry, "where, because of good managment, nutrition, animal health practices and sanitation,

> we cannot expect feed additive responses in terms of growth and feed efficacy for finishing hog?" His answer is a resounding, "yes," and corroborates Dr. Richard Novick's contention that in the practices of good modern animal husbandry the concomitant use of antibiotics produces no significant improvement in weight gain and feed efficiency. In the author's analysis of a recent trial, he finds that while it was statistically and economically advantageous to feed antibiotics up until the 120 pound stage, these advantages disappeared by the time the swine attained market weight.
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> The other article, by Drs. J.J. Shull and B.P. Cardon of Arizona Feeds, should alert farmers to the potential deleterious consequences of chronic antibiotic usage for their animals. It is an interesting documentation of the possible hazards posed by the resistant organisms generated by continuous feeding of drugs to livestock. In the U.S. enteropathogenic *E.coli* is generally resistant to amplicillin, neomycin, streptomycin, and the tetracyclines, the most commonly employed agents in commercial preparations used to feed young pigs and protect them from the problem of infectious diarrhea ("scours", caused by enteropathogenic *E.coli*). The authors articulate clearly how antibiotic treatment, rather than improving the problem of scours in the young pigs they observed, actually exacerbated it significantly. The incidence of cases of recurrent diarrhea was five-fold greater when oral antibiotics were employed for therapy than when they were not. Their conclusion: "the need for antibiotics in feed is not universal."

Few veterinarians have attempted to relate the development of clinical disease in animals to chronic "subtherapeutic" usage of these additives in feeding regimens. One report from Dr. C.A. Hjerpe describes a clear-cut example of therapeutic compromise in cattle. The organism responsible, *Pasteurella multocida*, known to cause pneumonia in cattle and on occasion to infect man, developed multiple resistance as as a result of the initiation of chronic chlortetracycline (CTC) feeding at the feedlot. According to Hjerpe,* "within a month, however, we had begun to observe increased numbers of pneumonic cattle which did not respond satisfactorily to treatment with the standard antimicrobics." The economic loss to the feedlot from antimicrobic-resistant pasteurella organisms was estimated to be $206,000, based upon increased mortality rates, culling rates, and medicine costs during this period of multiple resistance.

Dr. John Timoney, A Cornell University Professor of Vertinary Medicine and contributor to the 1980 NAS study, admits that antibiotic resistance due to improper use is a real problem in terms of refractory infections. He estimates (personal communication), from his own research efforts and his considerable experience in working with veal calf operations, that 60-70 percent of the enteropethogenic E.Coli and salmonellae are multiply resistant. This is a grave situation, he asserts, in terms of compromised antibiotic therapy when it becomes necessary to treat actual enteropathogenic illness, such as "scours."

It has become apparent to a small minority of farmers and hopefully will become clear to the members of Congress that what is being done here, using antibiotics to prevent disease in animals and to achieve a growth promotant effect, is doomed to failure. This is particularly true with the gram-negative bacteria, such as E.coli and Salmonella, where there is repeated fecal-oral transmission of strains and a large pool of transmissible R-plasmids. It bears reiterating, again and again, that the therapeutic arsenal available to physicians and veterinarians is a valuable, non-replenishable resource; once the causative bacteria become resistant to one or a number of drugs, the utility of these agents in treating the systemic disease is gone altogether or severely compromised.

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* Letter from Dr. C.A. Hjerpe to Dr. Stanley Falkow, Official Record of Hearings before the House Subcommittee on Oversight and Investigations, September 19 and 23, 1977; p. 134-136

Treatment failure is no trivial matter. As Dr. Stanley Falkow testified in 1977, resistant salmonella have killed people because of multiple antibiotic compromise. Again, one expects to hear the standard industry litany that there has never been a documented specific human case traceable to antibiotic usage in animals. We addressed the bankrupcy of this position earlier and do not wish to belabor the point. No one will ever be able to design a study showing that x number of people are refractory to medication or die each year as a result of having resistant organisms that arose from antibiotic dissemination to livestock.

According to Dr. John Bennett, an acknowledged expert in the field of infectious disease at the CDC, "perhaps as much as one-half of all salmonellosis is directly attributable to animal origins of salmonella."* Thirty to fifty percent of poultry available at the supermarket have salmonella that can be cultured. When one begins to consider the large proportion of drug-resistant salmonella in poultry and other food-producing animals, one recognizes the gravity of the situation. One percent of cases develop septicemia (30 percent mortality) out of 2.5 cases of salmonellosis identified each year. Since 30 percent of the patients suffering from septicemia on top of their salmonellosis initially were treated with the wrong drug because the causative organisms is refractory to the physician's drug of choice, there is obviously unnecessary morbidity and mortality. Just because it is impossible to ascribe a number to the relative contribution of animal antibiotic feeding does not mean the problem is any less real.

The literature and past testimony available to your Subcommittee are replete with scientific evidence that speaks extensively to our two main concerns: (1) the compromised human and animal antibiotic therapy, and (2) enhanced pathogenicity. While this is hardly the place for an indepth analysis of the entire field, we are compelled to re-emphasize certain scientific points which, in our opinion, were inadequately expressed in the course of your two sessions.

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* Official Record of the Hearings before the House Subcommitte on Oversight and Investigations, September 19 and 23, 1977; p. 189.

We hope the significance of the following remarks and citations is taken to heart by members of your Subcommittee and by the rest of the Congress. We apologize for any apparent redundancy, but additional comments are rendered by way of elaboration:

1. Industry pronouncements that resistant strains are not hardy and are overcome by wild types are specious. There is ample documentation that coliforms and other types bearing R-plasmids may persist in animals and in the environment for months after the selection pressure is removed. R-plasmids do not impose a significant metabolic burden on their hosts.

   On the human side, few careful prolonged monitoring studies of intestinal flora have been undertaken so that extensive data on the real life persistence of resistant strains and on R-plasmid transfer in the gut are relatively scarce. However, there is considerable evidence that antibiotic-resistant bacteria in animals can be transfered to humans. Hirsch* has also shown convincingly that human carriage of animal-derived resistant strains is greatly prolonged by the consumption of antibiotics, as might be seen in the adolescent using tetracyclines for acne.

2. Although hardly unique in its ability to foster multiple resistance, tetracycline appears to be unusually successful in this regard. Tetracycline selects for resistance not only to itself but also for the resistance to other antibacterials among both gram-negative and gram-positive bacteria.

3. FDA study has demonstrated that the incidence of multiple resistance in E.coli isolates was higher in herds exposed to continous feeding of antibiotics (85%) than not (15%).**

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* Hirsch, D., et al, Antimicrobial Agents and Chemotherapy, July 1973, p. 69-71

** Mercer, H.D., et al, Applied Microbiology, Oct. 1977, p. 700-705

Prior to 1948, 1% of Salmonella were resistant to tetracycline. In 1973, more than 40% were resistant.* Resistance in Salmonella strains has developed as follows:

Resistance of Salmonella to Number of Antibiotics	% Strains Resistant	
	1967	1975
1	41.1	69.4
2 or more	15.0	26.5
6 or more	0.8	9.2

4. The distinction drawn by industry between so-called "animal" and "human" strains of coliform bacteria is by and large bogus. Recognized non-partisan authorities speak of the free exchange of E.coli between animal species and man. Cross-colonization studies, serotyping, drug-resistance patterns, and plasmid DNA homology comparisons all attest to the extensive degree of host overlap. This is not to imply that all animal-derived E.coli that become exposed to the human gastrointestinal tract will successfully colonize, for this feat depends on many as yet poorly defined variables. It is important to understand, however, that there are few documented immutable barriers to the potential colonization of man.

5. While there is good scientific confirmation of the hypothesis that human exposure to medicated animal feed or to animals harboring drug-resistant bacteria results in an increased frequency of drug-resistant organisms in man, there are no documentations, in full epidemiological detail, of the exact amount of morbidity and mortality that can be attributed to subtherapeutic feeding. The NAS report, in essence, contended that such comprehensive documentation would be impossible. Such a rendering, we feel, is not required to make an informed public-policy decision on this issue.

   There are a number of reported cases of salmonellosis which can be traced to drug-resistant strains from animals. The role of animals and animal products as sources of Salmonella has been firmly established. For a more careful reading of the documented cases, we refer you to the official record of the 1977 Congressional hearings before the Subcommittee on Agricultural Research and General Legislation (p. 95 and following).

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* 43 Federal Register 3032 (January 20, 1978), at 3035

A number of studies* indicate a higher level of drug-resistant E.coli in people exposed to farm animals. This is significant since enteric illnesses due to refractory bacteria are more difficult to treat and eradicate, especially with regard to infant diarrhea - one of the leading causes of infant mortality world-wide.

One drug firm-sponsored investigation** compared hospitals located in agricultural and urban areas. The researchers found significantly greater percentages of resistance to tetracyclines, ampicillin, furazolidine and kanamycin in pooled isolates from rural Iowa patients than in those from an urban Connecticut hospital. More importantly, while chloramphenicol resistance was much greater in E.coli from the Connecticut patients, tetracycline and neomycin resistances were appreciably greater in Iowa patients. In all likelihood this reflects the pattern of antibiotic usage in animals. Tetracycline and neomycin are commonly employed as feed additives, whereas chloramphenicol is not approved by the FDA for use in animals, but is consistently used to treat hospital patients.

Another study*** found a high proportion of R-plasmid-carrying E.coli in infants admitted to a Dublin hospital. The babies had no history of previous hospitalization or antibacterial therapy. Attempts were made to discover whether the R-plasmids were common in rural and urban infants in Ireland. Numbers of infants excreting E.coli resistant to ampicillin, a cousin of penicillin, did not differ appreciably. However, a significantly higher fraction of E.coli (75%) were found resistant to chloramphenicol in the rural infants compared to the urban group (statistically very significant). At the time, chloramphenicol, the clear drug of choice for typhoid fever, was being used extensively by farmers in Ireland. The corresponding incidence of chloramphenicol resistance in urban populations was about 8 percent in either Dublin infants, London adults, or New York adults.

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* Smith I., 1974 Abstract 341 14th Interscience Conf. on Antimicrobial Agents and Chemotherapy, San Francisco, CA
Tschape, J., and Rische, H. 1974, Beit. Hyg. Epidemiol. 22: 1-102
Levy, S., New England Journal of Medicine 295: 583-588

** Langworth, B. and H. Jarolman, 1973 Progress Report 3-733 in American Cyanamid Company, submission of May 20, 1975 to FDA

*** Moorhouse, E. 1971 Annals of N.Y. Academy of Science 182, pp. 65-71 See also Moorhouse, E. 1961, Brit. Med. J. 2: 405-407.

Seventy percent of the infants with resistant bacteria were from families who had contact with livestock. Moreover, 66 percent of the infants carrying E.coli resistant to three or more antibiotics lived on farms, and all twelve infants excreting E.coli resistant to four or five drugs belonged to families who cared for livestock.

Now as we emphasized before, no one expects bacteria that are simply resistant to antibiotics to cause more infections than those that are not. Disease is usually a very complicated phenomenon and does not simply occur, although it can, when a certain organism invades one's person. There is a constellation of contributory factors, such as age, nutrition, status of the immune system, etc. Moreover, one can get disease "caused" by an organism that normally occupies the human body in a peaceful manner, e.g. Bacteroides. Carriage in infants of E.coli multiply resistant organisms, capable of causing infantile diarrhea if they possess or acquire the proper "virulence factors," poses a real hazard to the health of those infants, in terms of drastically reduced ability to treat effectively.

Moreover, as was stressed earlier, gram-negative enteric organisms such as E.coli are quite capable of transmitting their R-plasmids to truly pathogenic organisms, such as that responsible for bacterial meningitis. It has been clearly demonstrated that such notable pathogens can often survive long periods in their human niche without causing clinical disease. Many disease conditions are triggered by some change in the human host, leading to greater susceptibility, rather than by the arrival of an external agent. Clearly then, the presence and carriage of plasmid-bearing E.coli, fostered by human antibiotic therapy as well as by usage in animal feed, greatly increases the chances a person will play host or victim to a pathogenic resistant organ.

6. We emphasize that resistance is not the whole story. This point was not sufficiently covered in your recent hearings, and we ask that all members of the Subcommittee familiarize themselves with it by consulting the aforementioned paper of Dr. Richard Novick, authority on plasmid biology. The following synposes borrow liberally from that paper.

In certain situations, antibiotics in animal feeds select directly for resistant organisms capable of causing human disease and thus may lead directly to human illness.

(a) E.coli enterotoxin and diarrhea: The gene for the toxin responsible for E.coli diarrhea, a condition that causes considerable mortality in the very young worldwide, is carried by a transmissible plasmid. These plasmids have recently been found to acquire antibiotic resistant genes as well. Although single case documentation of the transfer from animals to man of such strains or of these plasmids has not been done, a number of food-borne outbreaks of E.coli diarrhea due to these toxin-producing varieties have been substantiated. In view of the unusual animal source of food-borne coliforms, it is extremely likely that food-producing animals were responsible.

The achievement of linking a resistance gene on the same plasmid as the toxin gene (known as a "virulence factor") means that subsequent antibiotic feeding selects directly for an increase in the number of bacteria that can produce this disease.

(b) Similarly, another E.coli virulence factor, known as colicin V, is also carried by a transmissible plasmid that has also been shown to acquire resistance genes. Although the role of colicin V in pathogenicity is not known precisely, it has been observed that bacteria making this substance are (1) more resistant to the body's natural immune system defenses, (2) much better colonizers of the human gut, and (3) much more frequently found in association with extra-intestinal E.coli infections such as fatal septicemias and urinary-tract infections than as normal residents of the colony.

In addition, as Dr. Novick points out, there is strong reason to believe that enhancement by colicin V of *E.coli* virulence is not species-specific, i.e., a given colicin V plasmid will be as effective in man as in livestock.

It bears repeating that *E.coli* septicemia is an extremely serious matter, with a case fatality rate of nearly 33%. While uncommon in healthy adults, it still accounts for some 50,000 deaths per annum. Moreover, although the case fatality rate dropped precipitously in the years following the introduction of antibiotics, it has risen once again in recent years to what it was in the pre-antibiotic era. Undoubtedly the bulk of *E.coli* septicemias are attributable to the usage of antibiotics in human therapy, but one cannot discount the likelihood that continous feeding of these drugs, and the profound levels of multiply resistant *E.coli* that this practice has spawned, contributes to the recent compromises in treating septicemia and other bacterial diseases.

(c) *Psittacosis*: The primary reservoir of this disease is birds, and domestic poultry is perhaps the most important component of that reservoir with respect to human disease. Most, if not all, human psittacosis is directly acquired from birds via breathing. There is little, if any, spreading from person to person. There are two way in whcih antibiotic feeding to poultry results in a human health hazard. First, subtherapeutic tetracycline supresses the symptoms of the condition (in turkeys) but fails to eliminate the organisms. Defeathering of the birds is probably the major mechanism of aerosol production, and workers are consequently infected by processing birds that appear clinically healthy. Second, in recent years, tetracycline resistant *Chlamydia psittacii*, the causative organism, has been isolated and has been transfered from turkeys to humans in a turkey processing plant. This is a clear choice of therapeutic compromise, since tetracycline is the drug of choice for this disease. Although most human cases present relatively minor respiratory complications, severe and fatal pneumonia can occur.

7. We request that members of the Subcommittee thoroughly scrutinize available data supporting the contention that the use of feed additive antibiotics makes animal disease more difficult to treat (see Appendix C of the FDA Task Force Report).

In a survey conducted involving over 100,000 cattle, the animals receiving feed additive antibiotics had a statistically significant higher incidence of respiratory disease than animals not fed them. This survey also demonstrated conclusively that the antibiotic fed animals had a higher death rate and a poorer response to therapy than the animals which did not. Translation: fiscal havoc.

Specific Comments on the Language of H.R. 7285:

As we mentioned at the outset, we embrace the rationale of this legislation. Substantive action is long overdue and while we hesitate to label the contribution by non-therapeutic usage of antibiotics in animal husbandry to the ever-icreasing pool of resistant bacteria an "imminent hazard", we are alarmed at the apparent lack of concern or recognition in Congress for the hazards such practice poses for the health of both man and beast. We fully endorse the philosophy that no antibiotics utilized in human therapy or which select[*] for organisms resistant to human drugs should be concomitantly employed for non-therapeutic purposes in animal husbandry. However, we believe also that it is critically important to curb the indiscriminate use of penicillins and tetracyclines, from all available evidence the most powerful selective forces for multiple resistance.

We offer the following suggestions for revising several of the provisions of H.R. 7285 which we believe are factually inaccurate or improperly stated:

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[*] For instance, tylosin, used in animal feed, selects for erythromycin-resistant staphylococci and streptococci. Erythromycin is an important drug for human therapy, being the drug of choice in those patients who need penicillin but are unable to receive it(allergic), or for certain illnesses like mycoplasma-related respiratory disorders.

> Section 2(2): the continuous use of these antibiotics for non-therapeutic* purposes has significantly increased the proportion of nonpathogenic and pathogenic bacteria in animals that are singly and multiply resistant to such antibiotics;
>
> Section 2(3): this growing pool of resistance poses a real yet unquantifiable threat to human and animal health, in terms of increasing the liklihood that an individual stricken with a serious disease (such as E.coli septicemia, meningitis, and salmonellosis) will find the available therapeutic armamentarium significantly compromised;
>
> Section 2(4): Delete as stands, and replace with:
>
> that along with excessive utilization of antibiotics by the medical profession, the policy of unrestricted use of antibiotics for non-therapeutic functions in livestock management will inexorably lead to a vitiation of our therapeutic resources and may well endow certain disease-causing bacteria with enhanced virulence;
>
> Section 2(5): replace "avoid" with reduce;"
>
> Section 2(6): the adoption of such a restriction in this country will help to reduce gradually the present intolerably high levels of antibiotic-resistant bacteria in the general pool, thereby reducing the risk to the public health by slowing the compromise of human antibiotics;
>
> Section 2(7): the adoption of such a restriction will not hinder the raising of livestock because there are numerous approved substitutes for the human antibiotics currently used in animal feeds.

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*Falkow, Novick, Bennett and others vigorously assert that the distinction between subtherapeutic and therapeutic dosage levels, in terms of ability to increase frequency of resistance is artificial. The true distinction should be non-therapeutic, where usage is chronic and not in response to real disease, and therapeutic, where usage is for short duration and high dose for treatment of overt diease.

In summary, the evidence indicates that gut bacteria in livestock and man, their R-plasmids, and human pathogens form a linked ecosystem in which action at any one point can affect every other. The susceptibility of bacteria to antibiotics is a kind of "commons" -- a resource which, if depleted by the use of such drugs for non-medical purposes in animals, will be diminished in man. Objective experts in this field agree overwhelmingly with this position.

This legislation is certainly no panacea for eliminating the widespread resistance problem. We believe strongly, however, that the restrictions that would be expeditiously afforded by prompt passage of this bill can improve the public safety substantially by eliminating what seems to us in practice a significant degree of unnecessary usage.

As Congressman Dingell has emphasized, this is decidedly a policy question which calls for prudent judgment. We feel that there was sufficient information to implement restrictions as early as 1972 and certainly by 1977. Congress cannot afford to continue sitting on this issue. Logic and science dictate that members of your subcommittee move with alacrity.

We appreciate this opportunity to present our comments.

Sincerely yours,

Karim Ahmed/cc
A. Karim Ahmed, Ph.D.
Senior Staff Scientist

Christopher Coley
Christopher Coley,
Research Assistant

AKA/CC:skb

ABDNOR
[illegible] SOUTH DAKOTA
[illegible] HOUSE OFFICE BUILDING
[illegible]

WALTER C. [illegible]
ADMINISTRATIVE ASSISTANT

COMMITTEES:
PUBLIC WORKS
AND TRANSPORTATION
VETERANS' AFFAIRS
AGING

Congress of the United States
House of Representatives
Washington, D.C. 20515

June 23, 1980

Rep. Henry A. Waxman, Chairman
Subcommittee On Health And The Environment
Committee On Interstate And Foreign Commerce
2415 Rayburn HOB

Dear Henry:

I would like to convey some thoughts on H.R. 7285, which would curtail the use of all antibiotics in animal feed.

South Dakota's acting Secretary of Agriculture, Mr. Rodger Pearson, argues that the Secretary of Health, Education and Welfare has the authority to ban any drug or additive which is found unsafe to human or animal health. The authority has been used in the past to restrict and/or ban several products from the market.

Mr. Pearson feels that there is no need for any new authority such as H.R. 7285, when in fact there is already adequate legislation on the books.

Drugs have been used extensively for the past three decades in animal production. About 70% of the animals receiving such antibiotics get them through feed supplementation for growth promotion and feed efficiency and about 40% of all antibacterial products produced in the United States are used in animal feeds.

It appears that the FDA considers the possible health risks from development of bacterial resistance to antibacterials in feed are of great concern and that other drugs from animal feeds could be used instead. Yet there is not valid scientific evidence that resistance to the antibiotics in the bacteria of the animals exist or if it does exist, that it is transferable to the bacteria in man under normal animal production.

The economic consequences of restricting or removing the antibiotics and other drugs from animal feeds could be significant. Livestock production may decline and consumer prices would be higher. With so many miles between towns and the few number of veterinarians in South Dakota, removal of antibiotics would make cattle raising prohibitive in many situations.

Thank you for your consideration. If possible, please include these remarks in the record of the Subcommittee's recent hearings on this important issue.

With best regards,

Sincerely,

JAMES ABDNOR
Member of Congress

JA/kb

[illegible] Rayburn Office Building
Washington, D.C. [illegible]
[illegible]

District Offices:
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Minot, North Dakota [illegible]
(701) [illegible]

Congress of the United States
House of Representatives
Washington, D.C.

MARK ANDREWS
North Dakota

COMMITTEE ON APPROPRIATIONS

Subcommittees:
Agriculture and Related Agencies
State, Justice, Commerce and Judiciary

June 25, 1980

Honorable Henry A. Waxman, Chairman
Subcommittee on Health and the Environment
House Interstate and Foreign Commerce Committee
2415 Rayburn House Office Building
Washington, D. C.

Dear Mr. Chairman:

It has come to my attention that your Subcommittee is holding hearings on H.R. 7285, the Antibiotics Preservation Act, co-sponsored by you and Congressman Dingell.

I would appreciate it if this letter could be made a part of the record. As you know, the Appropriations Committee has been vitally interested in the matter of subtherapeutic use of antibiotics in animal feed. For the last several years we have included language on the importance of gathering more reliable information on this matter in our report on the Agriculture Appropriations Bill. Enclosed you will find a copy of the language.

Because of our concern over the charges that had been made concerning the use of antibiotics, we appropriated funds for a study which was just recently completed by the National Academy of Sciences on "The Effects on Human Health of Subtherapeutic Use of Antimicrobials in Animal Feeds." I am enclosing a copy of that study for your review.

As you can see on Page 53 of this report, the study concluded that, "After reviewing the evidence, the Committee concluded that the postulations concerning the hazards to human health that might result from the addition of subtherapeutic antimicrobials to feeds have been neither proven nor disproven. The lack of data linking human illness with subtherapeutic levels of antimicrobials must not be equated with proof that the proposed hazards do not exist. The research necessary to establish and measure a definite risk has not been conducted..."

I contend that the legislation you are proposing is premature, and could, if enacted, be not only harmful to our livestock industry, but very costly to the American consumer in this time of ever increasing inflation. It has been estimated that the banning of the use of these subtherapeutic drugs in animal feeds would boost total meat expenditures by U.S. consumers over $1.2 billion a year.

It has been pointed out that these drugs have been administered at subtherapeutic levels to billions of animals in the U.S. for more than twenty-five years without any indication that human health has ever been adversely affected. To pass legislation based on theoretical risk at this time would set a precedent we would find very hard to live with in the future. If these drugs are banned because of theoretical risk, all animal health products could be banned for the same reason and there would be very little incentive for drug manufacturers to do further research to develop improved animal health products.

I am strongly opposed to this bill at this time. Further studies must be done before we take action that could be so harmful to the livestock industry and the consumer.

Best wishes.

Sincerely,

MARK ANDREWS
Congressman for North Dakota

MA:mab

cc: Congressman John Dingell

be on a trial and limited basis, the results of which should be made available to the appropriate committees of the Congress. Piecemeal and repeated changes should be avoided.

The Committee will expect the agency to work together with industry and consumers toward proper labeling at the lowest possible cost. In no instance should labels be required to state value judgments on the public health significance of product ingredients. The agency will be expected to notify the appropriate committees of the Congress prior to taking any action on food labeling.

PATIENT PACKAGE INSERTS

The FDA has proposed patient labeling of prescription drugs to provide consumers with more information. Proposed regulations would require that patient inserts accompany prescription drugs when dispensed by a pharmacist to a patient.

The agency should proceed only in an orderly, step-by-step manner, keeping the appropriate committees of Congress fully advised in advance of specific actions proposed. FDA will be expected to carefully and clearly establish priorities, evaluate existing materials and methods, and conduct appropriate research and pilot testing and evaluation. In considering available and potential alternatives, such as the U.S. Pharmacopoeia Dispensing Information, FDA shall thoroughly investigate cost implications and exercise caution that no unnecessary inflationary costs are imposed either directly or indirectly on consumers.

In testing the effectiveness and cost of patient package inserts and other approaches to provide consumers with information on prescription drugs, the Committee will expect FDA compliance with all assurances given during appropriations hearings. Included in these assurances were commitments to issue no more than ten package inserts during the next two years, to adhere to Administrative Procedure Act requirements for informal rulemaking proceedings, and to accurately determine and detail the costs to consumers and providers of prescription drugs. Such providers, according to FDA testimony, should not be required to distribute more than ten different package inserts under the test program.

ANTIBIOTICS IN ANIMAL FEED

The Food and Drug Administration has proposed to restrict the subtherapeutic uses of penicillin and tetracyclines for animal health purposes. Because it is important that technology in the production of food should not be abandoned without proven cause, Congress authorized FDA to contract with the National Academy of Sciences to review data on the subject, identify data gaps, and make recommendations for further action.

NAS has reported that "the postulated hazards to human health from the subtherapeutic use of antimicrobials in animal feeds were neither proven nor disproven." Although a single comprehensive study which would settle the issue was considered technically impractical, the need for studies of several kinds was specified. In noting the lack of available information, the expert NAS committee recommended "that future epidemiological studies . . . be carefully planned to fill gaps in our present knowledge and, especially to avoid the errors of ambiguous design and small sample size that have caused such difficulties in interpreting the data."

In view of the NAS recommendations, this Committee remains committed to the earmarking by FDA of $1.5 million in fiscal 1981 for research generating new epidemiological information. Such research should follow the specific suggestions of NAS.

FDA will be expected to continue to hold in abeyance any implementation of its proposal pending the final results of the above research and evidentiary hearings.

DRUG DEVELOPMENT

Testimony before the Committee has revealed that the U.S. spends more on health care than most other industrial nations. Yet, figures indicate that five nations have fewer deaths from cancer than the United States; 10 nations have a lower death rate from circulatory diseases; 16 nations do a better job of keeping babies alive in the first year of life; and 17 nations have a higher level of male life expectancy.

The Committee remains concerned that these conditions may result partly because other countries have drugs available for use which the United States does not. There apparently are a significant number of "uneconomic drugs," for which the potential market is not sufficiently lucrative for the pharmaceutical industry to recoup the large amounts of money necessary to meet federal requirements for development and testing.

A recent GAO report, entitled "FDA Drug Approval—A Lengthy Process That Delays the Availability of Important New Drugs," pointed out that FDA and the drug industry both contribute to the length of the drug approval process, and both need to work to speed it up. That report recommends ways FDA can expedite the process, and the Committee will expect the appropriate committees of Congress to be notified periodically on what progress FDA is making in this regard.

The bill includes such funds as may be necessary for FDA to conduct or promote the testing of drugs which (1) have been in use for several years in foreign countries. but not in the United States: (2) are vital to the health and well-being of a significant segment, however limited in number, of the population; or (3) are otherwise "uneconomic" for private industry to perform.

The Committee notes that statutory authority for this presently exists under the Public Health Service Act, which affirmatively authorizes drug development activity. It was under this authority that over twenty years ago the FDA Bureau of Biologics, then the Division of Biological Standards, investigated and developed the yellow fever vaccine, which was then turned over to the private sector for production. Any patent developed by FDA is registered in the name of the government and is available to all companies. It was through a similar effort that the U.S. Department of Agriculture developed and made available penicillin.

The bill includes such funds as may be necessary for FDA to conduct or promote the testing of drugs which (1) have been in use for several years in foreign countries, but not in the United States; (2) are vital to the health and well-being of a significant segment, however limited in number, of the population; or (3) are otherwise "uneconomic" for private industry to perform. The agency should call on industry to report in what instances and why they have not sought approval here for drugs available in other countries.

The Committee notes that statutory authority for this presently exists under the Public Health Service Act, which affirmatively authorizes drug development activity. It was under this authority that over twenty years ago the FDA Bureau of Biologics, then the Division of Biological Standards, investigated and developed the yellow fever vaccine, which was then turned over to the private sector for production. Any patent developed by FDA is registered in the name of the government and is available to all companies. It was through a similar effort that the U.S. Department of Agriculture developed and made available penicillin.

It is also the intention of the Committee that increased attention be given to the approval and testing of drugs for use in minor species of food-producing animals. Commercial drug producers are often unwilling to go to the expense of qualifying drugs which have only a limited market from which to recapture their investment, although the drugs may be greatly needed in growing "minor" farm animals, such as sheep, goats, ducks, rabbits, pheasant, trout and catfish.

ANTIBIOTICS IN ANIMAL FEED

Last year the Food and Drug Administration proposed to severely restrict the subtherapeutic uses of penicillin and tetracyclines for animal health purposes. In response to concerns over the absence of definitive data to confirm the theoretical basis of the agency proposal, the agency has contracted with the National Academy of Sciences to review and critique all information available on the subject.

Building upon that foundation, this Bill includes, and the agency shall earmark, at least $1.5 million for research generating new epidemiological information by comparing the health of humans with extensive exposure to animals, and/or their products, receiving antibiotics at the subtherapeutic level with the health of comparable individuals not so exposed.

The study shall be designed in consultation with qualified epidemiologists available through the National Academy of Sciences. Appropriate Congressional committees shall be informed of the study design and there shall be a reasonable period of time for Congressional comment prior to the initiation of the actual research. Such research and investigation shall then be performed on a contractual basis by a nongovernmental research organization qualified and experienced in the relevant and appropriate scientific disciplines.

The agency will be expected to continue to hold in abeyance any and all implementation of its proposal pending the final results not only of the research provided herein, but also of such evidentiary hearings as may result from the notices of opportunity for hearings that have been published by FDA.

BUILDINGS AND FACILITIES

1979 appropriation	$10,459,000
1980 budget estimate	4,372,000
Recommended in the bill	4,372,000
Comparison:	
1979 appropriation	−6,087,000
1980 budget estimate	--------

The bill includes $4,372,000 for FDA buildings and facilities, which is the full amount of the budget request and $6,087,000 less than appropriated in fiscal year 1979.

Commodity Futures Trading Commission

1979 appropriation	$15,304,000
1980 budget estimate	16,366,000
Recommended in the bill	16,366,000
Comparison:	
1979 appropriation	+1,062,000
1980 budget estimate	--------

The Commodity Futures Trading Commission (CFTC) administers the Commodity Exhange Act of 1936, as amended. The purpose of the Commission is to further the economic utility of futures markets by encouraging their efficiency, assuring their integrity, and protecting participants against abusive trade practices, fraud, and deceit. The object is to enable the markets to better serve their designated function in providing a price discovery mechanism and as a means of offsetting price risk. In properly serving these functions, the futures markets contribute toward better planning, more efficient distribution and consumption, and more economical marketing.

The Committee recommends the full amount of the budget request.

Farm Credit Administration

LIMITATION ON ADMINISTRATIVE EXPENSES

1979 appropriation	($10,575,000)
1980 budget estimate	(----------)
Recommended in the bill	(11,897,000)
Comparison:	
1979 appropriation	(+1,322,000)
1980 budget estimate	(+11,897,000)

The Farm Credit Administration supervises, examines, and provides facilities and services to a coordinated system of farm credit banks and associations making loans to farmers and their cooperatives. Services and facilities furnished by the Administration facilitate the operations of the several agencies and their progress toward farmer ownership. Typical services are: custody of collateral for bonds and debentures, assistance in financing and investments, credit analysis, development of land appraisal standard and policies, preparation of reports and budgets, and preparation and distribution of information on farm credit. All expenses of these activities are paid by assessments collected from the banks and associations of the farm credit system.

The Administration, originally created by Executive Order No. 6084 on May 27, 1933, was transferred to the Department of Agri-

TITLE V—RELATED AGENCIES

Food and Drug Administration

SALARIES AND EXPENSES

1978 appropriation	$276, 243, 000
1979 budget estimate	294, 304, 000
Recommended in the bill	289, 854, 000
Comparison:	
1978 appropriation	+13, 611, 000
1979 budget estimate	−4, 450, 000

The programs of the Food and Drug Administration (FDA) are designed to achieve a single overall objective: consumer protection. FDA's mission is to ensure that (1) food is safe, pure, and wholesome; (2) human and animal drugs, biological products, and medical devices are safe and effective; and (3) radiological products and use procedures do not result in unnecessary exposure to radiation.

To accomplish its mission, FDA sets food and product standards; evaluates the safety and efficacy of new drugs before they are marketed; conducts and sponsors research studies to detect health hazards and violations of consumer laws or regulations; informs business firms and consumers about FDA-related topics; works with State and local agencies to develop programs that will supplement or complement those of FDA; maintains surveillance over foods, drugs, and electronic products to ensure that they are safe, effective, and honestly labeled; and takes legal action where necessary to remove violative products from the marketplace and to prosecute firms or individuals that violate the law.

The committee recommends $289,854,000 for the salaries and expenses of the Food and Drug Administration. Approved were all the requested program increases for the regulatory processes and the important implementation of the Medical Device Amendments of 1976.

COSMETICS RESEARCH

The bill includes an increase of $300,000 above the budget request for additional cosmetics research.

ANTIBIOTICS IN ANIMAL FEED

The Food and Drug Administration has proposed to severely restrict the subtherapeutic uses of penicillin and the tetracyclines for animal health purposes as a result of the theoretical possibility that these uses could conceivably lead to human health problems caused by antibiotic-resistant bacteria. This proposal has major economic ramifications to consumers. The Congressional Office of Technology Assessment estimated recently that the banning of tetracyclines and penicillin in feed would increase the cost of meat to consumers by about $1,2[illegible],000,000 a year. OTA also reported that their calculations did not take into account the effect of substitutes for the banned antibiotics, although they note that the available substitute drugs are not as effective in hog, cattle and sheep production.

The Committee is pleased with the efforts of Commissioner Kennedy and the FDA in holding Regional public hearings in Ames, Iowa; Raleigh, North Carolina and Dallas, Texas, regarding the regulations for use of antibiotics in animal feeds, among those groups that would be subject to these proposed regulations.

At the same time, the Committee is concerned at the apparent lack of definitive data associating theoretical scientific concerns about the use of antibiotics in animal feeds with demonstrated human health problems.

There is strong disagreement among reputable scientists as to whether or not the continued subtherapeutic use of these antibiotics would result in any significant human health risk. Antibiotics have been administered at subtherapeutic levels to billions of animals in the U.S. for more than twenty-five years without any indication that human health has ever been adversely affected. There are those who argue that if there were any significant human health problems associated with such use, surely the problems would have developed during more than a quarter century of extensive and continuous use. Further, it is pointed out that there is theoretical risk connected with the use of every health product, whether used for animals or for man. If these antibiotics are banned on solely theoretical grounds, it might seem to establish a precedent so that most, if not all, animal health products could be banned for the same reason. Thus a serious potential problem could develop since, if animal health products can be banned because of theoretical risk, there might be very little incentive for drug manufacturers to do further research to test actual risks and to develop improved animal health products.

The committee recommends that research be done on this matter. In consideration of the scientific disagreement on this question, the possibility of establishing a precedent of banning products on theoretical grounds, and the potential added cost of billions of dollars to consumers, the committee can see no other responsible course of action to properly settle the matter. The bill includes $250,000 for this additional research, and FDA will be expected to hold in abeyance any and all implementation of their proposal pending the final results not only of the research provided herein, but also of such evidentiary hearings as may result from the notices of opportunity for hearing that have been published by FDA.

The objective of the research should be to compare the health of humans with extensive exposure to animals, and/or their products, receiving antibiotics at the subtherapeutic level with the health of comparable individuals not so exposed.

This research should logically be supervised and conducted by capable, objective scientists who have not already formed strong opinions as to whether or not these antibiotics should continue to be used at subtherapeutic levels for animals. Since FDA has already taken a strong position on the question, the committee urges that FDA contract with the National Academy of Sciences to plan and monitor the research.

FREEDOM OF INFORMATION ACT

Testimony before the committee shows that FDA spends $1,800,000 annually to comply with Freedom of Information Act requests while collecting only $122,000 in fees, which go to the Treasury. Studies have indicated that 84 percent of those requesting information under the FOI Act are in a position to benefit financially from the information. The number of FOI requests received each year continues to rise. In 1975, 13,000 requests were received. This year 28,000 requests, requiring about 85 staff-years of workload, will be processed.

The skilled professionals who conduct drug application reviews, for example, are the same people who must drop their program work to review freedom of information inquiries involving drug applications in order to protect trade secret information. With over 4,000 FOI annual inquiries relating to human drugs alone, this amounts to a sizable workload upon the drug application reviewers.

In view of this situation, the Department of Health, Education, and Welfare will be expected to develop a revised rate structure designed to more fully recover costs, while allowing sufficient flexibility for those truly not able to pay the additional costs.

ATTORNEY FEES

The committee is not convinced that paying the costs of consumer participation in this agency's regulatory activities would be an appropriate use of funds provided by the taxpayer for the implementation and enforcement of the Federal Food, Drug and Cosmetic Act and the other legislation administered by the FDA. The committee also notes the apparent absence of any definitive legislative intent as to a definition of what such representation should consist of and the extent to which it should be funded.

The payment of attorney fees for public interest advocacy should be postponed so that the appropriate committees of Congress may consider the question of whether to provide through legislation better definitions and limits suitable to the responsible use of public funds for this kind of purpose. Consequently, there are no funds in the bill for payment of such attorney fees, in accordance with Section 628 of Title 31 of the United States Code.

ADP FIELD INFORMATION SYSTEM

With regard to FDA's plans for a Field Information System, the committee will expect that system development be scheduled to allow for pilot testing of both new hardware and applications software in a limited number of locations before committing the Government to a major investment of money and personnel time. This testing should be against predetermined benchmarks of performance for both hardware and software. Full development should not be initiated until it can be shown that field and headquarters needs would be met by the new system at a lower cost than other alternatives. FDA should use a lowest-overall cost basis in evaluating system alternatives, and include all costs such as equipment purchase, personnel costs, software, training, installation, supplies, maintenance, telecommunications and parallel run costs.

American Farm Bureau Federation

WASHINGTON OFFICE
[illegible]
[illegible]
[illegible]
[illegible]

June 13, 1980

Honorable Henry A. Waxman, Chairman
Subcommittee on Health and the Environment
Committee on Interstate and Foreign Commerce
U.S. House of Representatives
Washington, D.C. 20515

Dear Mr. Chairman:

The American Farm Bureau Federation is the nation's largest voluntary general farm organization, comprised of more than 3.2 million member families in 49 states and Puerto Rico, including commercial producers of all species of livestock and poultry raised for human consumption.

This letter concerns H.R. 7285, the "Antibiotics Preservation Act of 1980" introduced in the U.S. House of Representatives on May 7, 1980 by Representative Dingell and you.

Farm Bureau participated in the administrative hearing process concerning the subtherapeutic use of antibiotics in animal feeds conducted by the Food and Drug Administration in 1978.

Two recommendations made at that time were as follows:

> "An epidemiological study should be conducted to monitor the status of health in humans, especially with regard to bacterial infections of livestock producers exposed to animals receiving antibiotics in their feed, as compared to persons not so exposed. This study needs to be continued for a sufficient period of time (perhaps five years) and must include enough human subjects to show a significant difference in the incidence of antibiotic resistant bacterial diseases between groups.
>
> "An epidemiological study should be undertaken on the prevalence and character of bacterial infections between matched groups of meat eaters and nonmeat eaters and between matched groups of workers, such as butchers, who have occupational exposure to meat and workers who do not have such exposure."

Congress appropriated funds for the Food and Drug Administration to carry out this type of scientific research. Congress further stipulated that FDA hold in abeyance implementation of proposals to ban the use of penicillin and tetracyclines in animal feeds until the research is completed.

FDA is currently evaluating research needs and is prepared to implement additional research.

We believe the existing regulatory structure and authorities within FDA are adequate to balance and protect the interests of public health and the agricultural user of antibiotics. Therefore, we oppose H.R. 7285 and urge this Subcommittee to encourage and support FDA research projects aimed at achieving enhanced scientific evaluation of the effects on human health, if any, associated with subtherapeutic use of antibiotics in livestock and poultry.

We request that this letter be made a part of the hearing record.

Sincerely,

Vernie R. Glasson, Director
National Affairs Division

COVINGTON & BURLING
888 SIXTEENTH STREET, N.W.
WASHINGTON, D.C. 20006
[illegible]
WRITER'S DIRECT DIAL NUMBER
(202) 452-6300

July 2, 1980

The Honorable Henry A. Waxman
Chairman, Subcommittee on
  Health and the Environment
House Committee on Interstate and
  Foreign Commerce
Room 2415 Rayburn House Office Building
Washington, D.C. 20515

RE: H.R. 7285 "Antibiotics Preservation Act"

Dear Mr. Chairman:

These additional views are submitted on behalf of the Animal Health Institute for inclusion in the hearing record on H.R. 7285 in accordance with the leave granted when I testified on behalf of the Institute concerning H.R. 7285 on June 12. The Animal Health Institute believes that the testimony of Dr. Crawford on behalf of the Food and Drug Administration presented June 24, 1980, supports the position taken by the Institute that the proposed legislation is both unnecessary and unwise.

First, Dr. Crawford specifically acknowledges that FDA "has. . . sufficient authority to take action against products such as those that pose a hazard to human health." [Statement, page 10.] As we urged before, this admission alone is a sufficient basis for objecting to the passage of unnecessary regulatory authority.

Second, Dr. Crawford notes that "over the past few years we [FDA] have been proceeding to implement this authority." He goes on to urge that the bill be amended to clarify that regulations issued under it would automatically revoke existing approvals: "Otherwise the bill would offer nothing over current law." [Statement, pages 10, 12.] Dr. Crawford thus acknowledges that the sole purpose of the bill is to permit FDA to avoid what he characterizes as a "lengthy and resource-intensive formal evidentiary hearing." Congress has nonetheless carefully provided that such hearings be held before approvals are revoked in order to assure that FDA action is based on supportable scientific evidence and not speculation and conjecture. We object strongly to any proposed legislation that would circumvent the controls and protections provided by Congress in the Animal Drug Amendments of 1968, particularly where, as here, they appear aimed at a specific group of drugs.

We appreciate the opportunity to present these supplemental views in opposition to the enactment of H.R. 7285.

Very truly yours,

Eugene I. Lambert
Counsel to
Animal Health Institute

[Whereupon, at 1:10 p.m., the hearing was adjourned.]

APPENDIX

Chase
Econometric
Associates
inc

ECONOMIC IMPACT STUDY:
EFFECTS OF A PROHIBITION ON THE USE OF SELECTED ANIMAL DRUGS

prepared for:

American Cyanamid
Diamond Shamrock Corporation
Merck and Company, Inc.
Rachelle Laboratories, Inc.
Pfizer, Incorporated

by:

CHASE ECONOMETRIC ASSOCIATES, INC.
555 City Line Avenue
Bala Cynwyd, Pennsylvania

October 1979

THE ECONOMIC IMPACT OF PROHIBITING THE USE OF SELECTED ANIMAL DRUGS

INTRODUCTION

The central issue this analysis addresses is "what is the economic impact on livestock producers, U.S. consumers, and the U.S. economy if a ban were ordered on the subtherapeutic use of selected animal drugs?" The specific economic impacts considered are:

(1) changes in livestock production and subsequent retail meat supplies,

(2) effects on producer prices, costs of production, and profits,

(3) changes in wholesale and retail meat prices,

(4) impact on the demand, production and prices of feed grains,

(5) changes in farm cash receipts and net farm income,

(6) changes in key macroeconomic variables such as the Consumer Price Index (CPI), unemployment rate, and Gross National Product (GNP), and

(7) effects on output and employment in the food industry and various sectors of the U.S. economy.

Basic technological data on the animal production effects of subtherapeutic drug use in livestock and poultry production are essential to a study such as this. Because the available technological evidence on the animal production effects of drug use are not conclusive, two levels of drug efficacy were assumed. Thus the analysis was performed under two assumptions--a moderate drug efficacy level and a high drug efficacy level. The moderate efficacy assumption utilized the low end of the range in technological effects of drug use, while the high efficacy assumption utilized the upper end of the range in technological effects of drug use. Thus, for example, the initial cumulative effect of a restriction on the use of the drugs in question in broiler production would be a reduction of 8.3% and 21.0% from levels without a ban under the moderate and high efficacy assumptions, respectively.

best copy available

SUMMARY OF CONCLUSIONS

(1) A ban on the use of selected subtherapeutic animal drugs would have a significant impact on the agricultural and U.S. economy during the initial year of the ban:

	Moderate Efficacy[1]	High Efficacy[1]
Meat and eggs		
Output	-3.0%	-9.2%
Farm prices	+5.3%	+14.9%
CPI, Food	+1.3%	+3.7%
CPI, All Items	+0.3%	+0.8%
GNP, 1972$	-0.1%	-0.3%
Unemployment Rate	+0.4%	+1.16%

(2) At the end of the second year, higher livestock prices will stimulate farmers to adjust production back toward the pre-ban level; however, meat production would still be 2.3% and 6.8%, respectively, below the baseline projections.

(3) The poultry industry is most dramatically influenced by a proposed ban. The broiler sector actually remains 3.8% and 10.0% below baseline production projections at the end of five years. Turkey production would still be 3.2% and 8.7% below pre-ban production levels by the end of five years. Wholesale prices for broilers and turkeys as a result would be 5% and 3%, respectively, higher under the "moderate" assumption and 10% and 8% higher, respectively, under the "high" assumption.

(4) The impact on egg production and prices is less severe than other segments of the poultry sector. Under the moderate efficacy assumption,

---

[1] Percent changes from the pre-ban level of economic activity

egg output would be readjusted to near baseline levels by the third year. Under the high efficacy assumption, egg output would actually be 0.4% higher by the second year than the baseline levels. Egg prices, however, would be 2.0% and 5% higher five years after a ban primarily because of high prices for competing meats, rather than lower egg output.

(5) A ban would have little impact on beef production by the second year because of this sector's relatively smaller utilization of these drugs.

(6) The pork industry, however, remains 1.1% below pre-ban production levels even four to five years later under the moderate assumption. Under the high assumption producers do not return to within 8% of baseline by the fifth year. Hog prices subsequently would average 2.0% and 9.6% above baseline prices.

(7) Demand for feed grains is weakened causing a feed grain price decline. The lower feed grain prices would cause an acreage shift between crops and a decline in feed grain production. By the fifth year feed grain acreage would be expected to decline 40 thousand acres under the moderate assumption and 440 thousand under the high assumption.

(8) Retail food prices would advance by 1.2% and 3.5% by the second year following a ban. The overall CPI would advance by 0.3% and 0.9% under the two different efficacy assumptions. Current dollar GNP declined 0.2% and 0.6% by the second year. Real personal disposable income would be $1.5 billion and $5.0 billion lower.

(9) It would require four years before the U.S. economy would reach a new equilibrium at a level consistent with the baseline projection. But even then GNP would be 0.5% lower than baseline while the overall CPI would be 0.3% above baseline, under the assumption of high efficacy.

(10) Under the moderate efficacy scenario, cash receipts to livestock producers would increase 1.6% annually over the five years studied while crop cash receipts would fall 0.6% annually. However, because the change in livestock receipts exceeds those of crops, net farm income increased 3.5% annually during the five years.

(11) The unemployment rate would increase by 0.4% during the first year and 1.1% to 1.4% during the remaining four years under the moderate efficacy assumption. Assuming a high efficacy, however, the unemployment rate would be expected to increase 1.2% in year one and 3.3% to 4.5% during the following four years.

TABLE 1

IMPACT UPON SELECTED ECONOMIC VARIABLES
PROJECTIONS AND PERCENTAGE CHANGES
FROM BASELINE PROJECTIONS FOR FIVE YEARS AFTER BAN OF SELECTED ANIMAL DRUGS BEGINNING IN 1980, MODERATE AND HIGH EFFICACY

	Year 1	2	3	4	5
	----------------	Moderate Efficacy	----------------		
Meat production,[1] bil. lbs.	57.28	58.30	59.63	62.38	63.71
% change	-3.0	-2.3	-1.2	-0.8	-0.5
Livestock Prices, Farm, 1967=100	284	293	294	321	344
% change	+5.3	+4.4	+1.9	+0.3	-0.4
CPI, Food, 1967=100	257	275	294	316	340
% change	+1.3	+1.2	+0.6	+0.2	-0.1
CPI, All Items, 1967=100	235	253	270	288	308
% change	+0.3	+0.3	+0.2	+0.1	-0.0
Real GNP, 1972$	1411	1455	1515	1579	1624
% change	-0.1	-0.2	-0.2	-0.1	-0.1
	----------------	High Efficacy	----------------		
Meat production,[1] bil. lbs.	53.58	55.63	57.94	61.90	61.86
% change	-9.2	-6.8	-4.0	-3.1	-3.4
Livestock Prices, Farm, 1967=100	310	313	306	328	352
% change	+14.9	+11.6	+5.9	+2.4	+ 2.0
CPI, Food, 1967=100	263	281	298	319	343
% change	+3.7	+3.5	+1.71	+0.9	+ 0.9
CPI, All Items, 1967=100	236	254	271	289	308
% change	+0.8	+0.9	+0.6	+0.3	+0.2
Real GNP, 1972$	1409	1449	1509	1573	1618
% change	-0.3	-0.6	-0.6	-0.5	-0.5

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[1] Includes beef, veal, pork, broilers, turkeys and eggs

PROCEDURE

Banning subtherapeutic drugs from animal feed slows animal growth rates, increases product condemnation and increases animal mortality. Economically, we would expect production to decline and prices to rise. (See Appendix A for a more thorough theoretical discussion.)

Estimates for the technical responses on growth rate, product condemnation and mortality if certain drugs were banned were obtained from the USDA, land grant universities, veterinarians, and private publications. The estimated changes in livestock output from banning selected drugs were taken from a USDA analysis, table 2.[1] This analysis, as ours, assumes no alternative drugs were available. The estimated impacts were made for fed beef, pork, broilers, eggs, and turkeys, and include a "low" and "high" impact range, hereafter referred to as "moderate" and "high" efficacy. These data provided the production coefficients needed to analyze the impact of a drug ban.

Changes in the production coefficients were exogenously simulated through the supply-side of the CEAI agricultural model to measure the impact of a selected drug ban on livestock, grains, oilseeds, farm income, etc. Results from these simulations were, in turn, entered into CEAI's U.S. macroeconomic model and CEAI's input-output model to measure the impact of a selected drug ban on the consumer sectors and other major sectors of the economy. We were thus able to instigate changes in the supply side, for example, and evaluate its impact not only on the price of beef, but also on

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[1] ESCS, USDA, "Economic Effects of a Prohibition on the Use of Selected Animal Drugs."

TABLE 2

ESTIMATED PERCENTAGE CHANGE IN LIVESTOCK PRODUCT OUTPUT FROM BANNING SELECTED DRUGS IN SUBTHERAPEUTIC USES MODERATE AND HIGH DRUG EFFICACY, FIRST YEAR (1976)[1]

Animal Species	Penicillin		Tetracyclines		Nitrofurans[2]		Sulfa[3]		Cumulative Effect	
	Moderate	High	Moderate	High	Moderate	High	Moderate	High	Moderate	High
	percent									
Fed beef cattle	NA	NA	-0.4	-0.8	NA	NA	NA	NA	-0.4	-0.8
Hogs	NA	NA	-3.4	-15.6	NA	NA	-1.5	-2.2	-4.9	-17.8
Broilers	-2.1	-3.8	-6.4	-11.5	0.2	-5.7	NA	NA	-8.3	-21.0
Egg production	-0.6	-1.0	-1.2	-2.3	0.1	-0.3	NA	NA	-1.7	-3.6
Turkeys	-1.4	-2.8	-2.8	-4.6	-1.9	-8.7	NA	NA	-6.1	-16.1

Source: ESCS, USDA, "Economic Effects of a Prohibition on the Use of Selected Animal Drugs."

NA = not applicable

[1] The higher the expected response to a feed additive, the greater the reduction in output if the additive is banned.

[2] In poultry, it is possible to get a slight increase in output when nitrofurans are removed from the feed.

[3] The major effect would be the sulfa drugs, but would also include the effects attributed to penicillin and the tetracyclines.

other livestock products, feed, the food industry, and other sectors of the economy.

The CEAI "Long Term Agricultural Forecast" was used as the baseline projection. Then livestock production changes were simulated for a five-year period, 1980-1984, under two scenarios, a ban at both the moderate and high efficacy levels. As a result final changes in livestock production in any time period is the result of both "physiological" changes in growth rates, mortality, etc., and producers' responses to their changing cost-price structure. The USDA study provided estimates of the physiological changes; hence, the difference between the exogenously imposed physiological differences and the final production estimates can be explained as the expected producer economic reaction to a selected drug ban.

Results from the agricultural scenarios (farm, wholesale, and retail food prices, farm income, etc.) were imposed upon the CEAI U.S. macroeconomic model to simulate effects upon the overall economy. Changes in inflation, disposable income and Gross National Product were thus estimated. In order to capture even greater detail of the economic repercussions of these alternative situations, both the estimated impacts upon the agricultural economy, from the agricultural simulations, and the estimated impacts upon the total U.S. economy, from the macroeconomic simulations, were imposed upon the CEAI long-term interindustry input-output model. As a result of the dynamic input-output structure of the model, it details not only the direct impact of the proposed ban on the livestock, poultry and meat product sectors, but quantifies the indirect effects as well. Thus the changes in output and employment by industry can be estimated.

DISCUSSION OF RESULTS

Initially, imposing a ban on selected animal drugs causes meat output to fall by 3% under the moderate efficacy assumption and 9% under the high efficacy assumption. Farm prices as a result advance 8% and 19.6%, respectively. Retail meat prices rise and per capita consumption of meat falls 3.0% and 9.7%, respectively, under the moderate and high efficacy assumptions. The impact of the ban then reverberates throughout the economy causing the CPI for food to rise 1.5% and 3.5%, and the CPI for all items to increase 0.3% and 0.8%. Real GNP (1972 dollars) falls by $1.3 billion and $3.8 billion, respectively. Manufacturing employment falls by 5 thousand and 18 thousand, in turn increasing the unemployment rate by 0.4% and 1.0% during year one.

By the second year, higher farm prices will stimulate farmers to adjust their production back toward the pre-ban levels. Thus, meat production reductions from baseline in year two following the ban would still be 2.3% and 6.8% from the baseline. However, this production adjustment process requires several years to complete with the adjustment rate varying greatly between the moderate and high efficacy assumptions as well as among livestock enterprises. For example, beef production would recover near to baseline projections by the second year because of this sector's relatively smaller utilization of these drugs. Pork and poultry production, in contrast, remain below baseline production levels, even five years later. As a result, pork and poultry prices would continue advancing because of the reduced supplies.

The initial reduction in livestock numbers caused by imposing the ban forces the demand for corn to decline about 1%, corn inventories to increase 4.4% and prices to fall 0.3% under the moderate efficacy assumption. Soybean meal consumption, on the other hand, drops 4.9%, inventories jump 11%, and Chicago soybean meal prices drop about 4.5% under the moderate assumption. It would take approximately four to five years before the grain sector would reach an equilibrium state similar to the pre-ban era.

The aggregated impacts on the U.S. economy are significant, especially in year two when the CPI for food advances 1.2% and 3.5% under the moderate and high efficacy assumptions. In turn the overall CPI would advance 0.3% and 0.9%. Current dollar GNP would decline by 0.2% and 0.6%, respectively, during the second year with real personal disposable income declining by 0.14% and 0.5% or, in 1972 dollars, $1.5 billion and $5.1 billion.

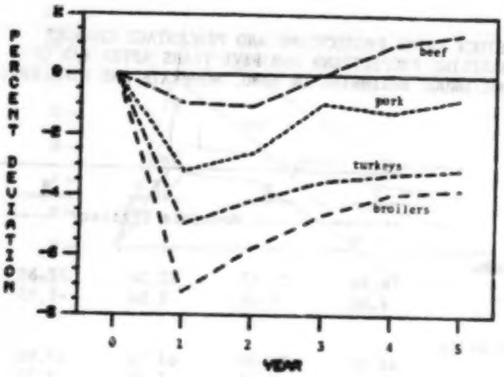
Using the Consumer Price Index for all items and GNP as measures, the economy under the moderate efficacy scenario settles down to a new equilibrium by the fourth year with current dollar GNP 0.1% ($2.6 billion) below baseline, constant dollar GNP 0.1% ($1.8 billion, 1972$) below baseline, and the CPI 0.1% above baseline. By the fourth year under the high efficacy scneario current dollar GNP would be expected at 0.3% ($11.7 billion) below baseline, constant dollar GNP 0.5% ($8.4 billion, 1972$) below baseline, and the CPI averaging 0.3% above baseline. The unemployment rate by the fourth and fifth years would be expected to average approximately 3.8% (or 0.2 percentage points) above baseline.

TABLE 3

LIVESTOCK PRODUCTION PROJECTIONS AND PERCENTAGE CHANGES FROM BASELINE PROJECTIONS FOR FIVE YEARS AFTER BAN OF SELECTED ANIMAL DRUGS BEGINNING IN 1980, MODERATE AND HIGH EFFICACY

	Year				
	1	2	3	4	5
	Moderate Efficacy				
Fed Beef, bil. lbs.	17.28	17.75	18.55	18.71	18.80
% change	-0.90	-0.18	0.10	-0.28	-0.59
All Beef & Veal, bil. lbs.	21.15	22.30	24.31	25.28	25.30
% change	-0.97	-1.05	0.0	1.01	1.42
Pork, bil. lbs.	15.09	14.42	13.19	13.92	14.88
% change	-3.20	-2.60	-0.95	-1.24	-0.78
Broilers, bil. lbs.	10.27	10.64	11.08	11.93	12.31
% change	-7.25	-5.78	-4.64	-3.93	-3.77
Turkeys, bil. lbs.	2.09	2.16	2.24	2.40	2.31
% change	-4.97	-4.17	-3.53	-3.29	-3.11
Eggs, mil. cases	184.7	186.8	187.4	188.3	189.5
% change	-1.48	-0.43	0.10	0.17	-0.22
	High Efficacy				
Fed Beef, bil. lbs	17.39	18.00	18.84	19.12	19.23
% change	-1.43	0.05	0.55	0.75	0.57
All Beef & Veal, bil. lbs.	20.92	21.98	24.34	25.60	25.51
% change	-2.05	-2.48	0.12	2.30	2.23
Pork, bil. lbs.	13.16	13.20	12.43	13.11	13.81
% change	-15.60	-10.85	-6.66	-6.98	-7.90
Broilers, bil. lbs.	9.03	9.56	10.21	11.13	11.50
% change	-18.40	-15.29	-12.13	-10.39	-10.09
Turkeys, bil. lbs.	1.91	2.04	2.11	2.24	2.17
% change	-13.44	-9.39	-9.05	-9.65	-8.73
Eggs, bil. cases	182.1	188.3	188.3	187.7	188.7
% change	-2.86	0.37	0.57	-0.12	-0.68

PRODUCTION DEVIATIONS FROM BASE PROJECTIONS
FOR FIVE YEARS FOLLOWING BAN
MODERATE EFFICACY



PRODUCTION DEVIATIONS FROM BASE PROJECTIONS
FOR FIVE YEARS FOLLOWING BAN
HIGH EFFICACY

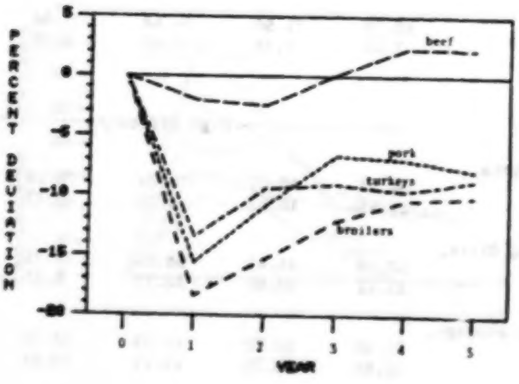
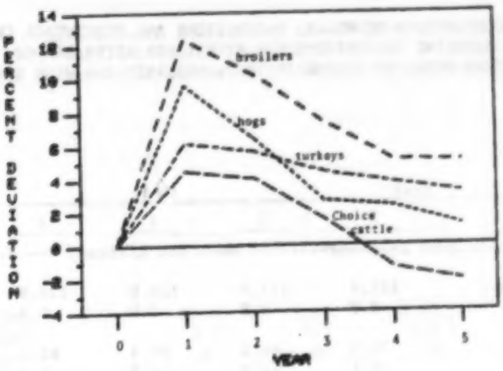


TABLE 4

LIVESTOCK PRICE PROJECTIONS AND PERCENTAGE CHANGES FROM BASELINE PROJECTIONS FOR FIVE YEARS AFTER BAN OF SELECTED ANIMAL DRUGS BEGINNING IN 1980, MODERATE AND HIGH EFFICACY

	Year 1	Year 2	Year 3	Year 4	Year 5
	---------- Moderate Efficacy ----------				
Choice Steers, Omaha, $/cwt.	78.96	75.67	72.30	77.85	88.09
% change	4.50	4.06	1.59	-1.33	-2.11
Hogs, Barrows and Gilts, Omaha, $/cwt.	46.36	56.30	63.12	67.98	67.96
% change	9.62	6.44	2.70	2.37	1.21
Broilers, 9-city average, ¢/lb.	48.18	51.75	58.24	55.27	58.01
% change	12.38	10.24	7.45	5.16	5.07
Turkeys, Hens, NY, ¢/lb.	62.12	67.33	69.43	66.38	71.94
% change	6.18	5.67	4.44	3.79	3.19
Eggs, NY, ¢/doz.	69.79	71.50	74.64	77.54	79.40
% change	7.30	4.58	2.65	1.98	2.00
	---------- High Efficacy ----------				
Choice Steers, Omaha, $/cwt.	84.50	80.01	74.04	78.29	89.55
% change	11.83	10.03	4.03	-0.77	-0.49
Hogs, Barrows and Gilts, Omaha, $/cwt.	57.15	65.42	68.08	72.75	73.68
% change	35.12	23.69	10.77	9.55	9.72
Broilers, 9-city average, ¢/lb.	53.80	56.70	61.33	58.24	61.00
% change	25.49	20.78	13.16	10.81	10.49
Turkeys, Hens, NY, ¢/lb.	67.93	71.61	73.72	71.00	75.19
% change	16.11	12.38	10.90	11.01	7.86
Eggs, NY, ¢/doz.	75.22	72.73	76.14	79.98	81.80
% change	15.64	6.39	4.71	5.19	5.09

PRICE DEVIATIONS FROM BASE PROJECTIONS
FOR FIVE YEARS FOLLOWING BAN
MODERATE EFFICACY



PRICE DEVIATIONS FROM BASE PROJECTIONS
FOR FIVE YEARS FOLLOWING BAN
HIGH EFFICACY

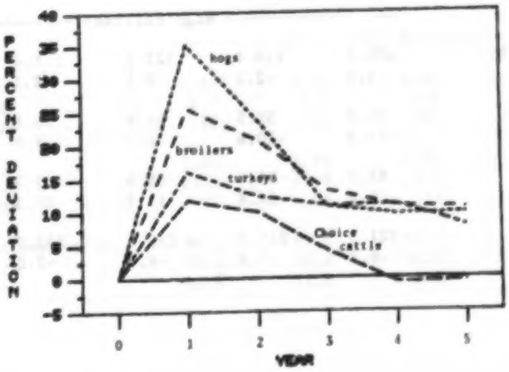


TABLE 5

PER CAPITA CONSUMPTION OF MEATS, PROJECTIONS AND PERCENTAGE CHANGES FROM BASELINE PROJECTIONS FOR FIVE YEARS AFTER BAN OF SELECTED ANIMAL DRUGS BEGINNING IN 1980, MODERATE AND HIGH EFFICACY

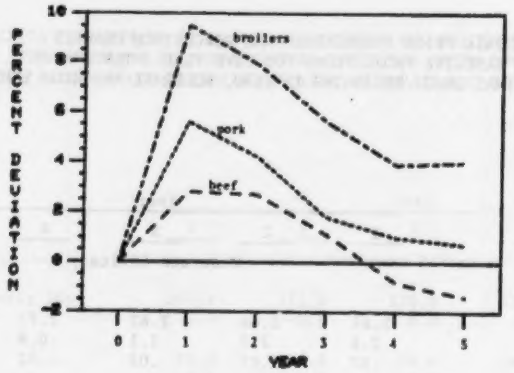
	Year				
	1	2	3	4	5
	Moderate Efficacy				
Beef and Veal, lbs.	107.4	111.8	120.9	124.9	124.8
% change	-0.9	-0.9	0.0	0.9	1.3
Pork, lbs.	70.0	65.5	59.4	62.2	66.0
% change	-3.1	-2.6	-1.0	-1.2	-0.8
Poultry, lbs.	60.2	61.1	63.1	67.2	68.3
% change	-6.5	-5.6	-4.4	-3.8	-3.6
TOTAL	237.6	238.5	243.4	254.3	259.1
% change	-3.0	-2.7	-1.4	-0.9	-0.6
	High Efficacy				
Beef and Veal, lbs.	106.4	110.4	121.1	121.4	125.7
% change	-1.8	-2.2	0.1	2.1	2.0
Pork, lbs.	61.2	59.9	55.9	58.6	61.3
% change	-15.3	-10.8	-6.7	-7.0	-7.9
Poultry, lbs.	53.7	55.4	58.3	62.7	63.8
% change	-16.6	-14.4	-11.7	-10.3	-9.9
TOTAL	221.3	225.7	235.3	247.7	250.8
% change	-9.7	-7.8	-4.7	-3.5	-3.8

TABLE 6

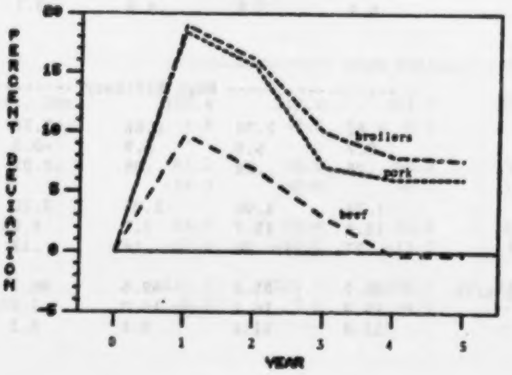
RETAIL PRICE PROJECTIONS AND PERCENTAGE CHANGES FROM BASELINE PROJECTIONS FOR FIVE YEAR AFTER BAN OF SELECTED ANIMAL DRUGS BEGINNING IN 1980, MODERATE AND HIGH EFFICACY

	Year				
	1	2	3	4	5
	Moderate Efficacy				
Beef, $/lb.	2.65	2.64	2.61	2.77	3.09
% change	2.8	2.7	1.1	-0.8	-1.4
$ change	.07	.07	.03	-.02	-.04
Pork, $/lb.	1.55	1.71	1.95	2.09	2.13
% change	5.6	4.2	1.8	1.0	0.7
$ change	.08	.07	.03	.02	.01
Young Chicken, ¢/lb.	73.8	79.4	86.0	83.0	86.7
% change	9.5	7.9	5.6	3.9	4.0
¢ change	6.4	5.8	4.6	3.1	3.3
	High Efficacy				
Beef, $/lb.	2.83	2.74	2.66	2.78	3.12
% change	9.7	6.9	2.9	-0.3	-0.3
$ change	.25	.18	.08	-0.01	-0.01
Pork, $/lb.	1.74	1.90	2.05	2.20	2.24
% change	18.4	15.5	7.1	6.0	6.0
$ change	.27	.26	.14	.12	.13
Young Chicken, ¢/lb.	80.2	85.4	89.6	86.1	89.8
% change	19.0	16.1	10.0	7.9	7.6
$ change	12.8	11.8	8.1	6.3	6.4

RETAIL PRICE DEVIATIONS FROM BASE PROJECTIONS
FOR FIVE YEARS FOLLOWING BAN
MODERATE EFFICACY



RETAIL PRICE DEVIATIONS FROM BASE PROJECTIONS
FOR FIVE YEARS FOLLOWING BAN
HIGH EFFICACY



Beef

The "technological" impact of lighter average live weights for fed cattle was imposed upon the fed-cattle sector. Under a ban scenario, the technological impact estimated by the USDA study was a reduction in average live weight from 1,062 pounds to 1,050 pounds under moderate drug efficacy and 1,038 pounds under high drug efficacy.

Because the direct impact of a ban is upon fed cattle only, the subsequent percentage change in total beef supply depends quite heavily upon the proportion of fed to non-fed cattle in the total beef supply. The fed to non-fed mix in cattle slaughter changes dramatically through various stages of the ten-year cattle cycle. During the first part of a liquidation stage, such as the period 1975 thorugh 1977 (the entire liquidation stage is defined as 1975 through 1979), producers are reducing cattle herds. Non-fed slaughter subsequently makes up an unduly high proportion of the total beef supply and, thus, fed beef represents an unusually small portion.

During 1976 (the one-year period of the USDA study) total cattle slaughter was made up of 58.7% fed slaughter and 41.3% non-fed slaughter. This compares to a slaughter mix of 70.2% fed and 29.8% non-fed during 1978 and an anticipated 1980 slaughter mix of 80.0% fed and 20.0% non-fed. Thus, the initial impact on total beef supplies of a 12-24 pound decline (1,050-1,038 and 1,062-1,038) in average dressed weight in fed cattle would be much greater based upon the 1980 cattle situation, than it would be based upon the cattle slaughter situation of 1976. Thus, the initial impacts on total beef output expected during 1980 based upon the estimated weight changes are -0.57% under moderate efficacy and -1.14% under high efficacy, versus -0.4% and -0.8% estimated by the USDA for 1976.

During the first year of a ban cattle feedlot operators have little opportunity to respond to the new economic situation. In addition, the fastest production response to higher beef prices can be negative, in as much as higher prices and potential profits will act to reduce non-fed cattle slaughter to increase further beef production. Thus, total beef and veal production would be expected to decline by 0.9% and 2.1%, respectively, during the first year under the moderate and high efficacy scenarios. These supply changes together with reduced supplies of pork and poultry would be expected to increase cattle prices by 4.5% and 11.8%, respectively, the first year. This beef response is quite significant because beef demand is relatively inelastic and beef prices receive additional upward boost from relatively sharper supply reductions in pork and poultry. Retail beef prices in the first two years would be expected to rise to $2.83 and $2.74/lb. under the high scenario, 27¢ and 24¢/lb. above baseline.

Because beef prices increase dramatically and because the "technological" influences on beef output are relatively small, beef production returned to near baseline projections in three years. Under the moderate efficacy scenario, total beef output increased to within 0.1% of baseline by year three, and under the high efficacy increased to within 0.1% of baseline by year two. In fact, initial higher beef prices are expected to boost total beef output over baseline levels in years four and five under both moderate and high scenarios, table 3, thus reducing cattle prices below baseline levels in both scenarios during years four and five. However, this decline is slight (-0.5% to 2.1%) because of reduced supplies of competing pork and poultry products.

TABLE 7

COST OF PRODUCTION AND NET RETURNS TO CORN BELT CATTLE FEEDING*

	Moderate Efficacy						High Efficacy					
	No Ban			Ban			No Ban			Ban		
1980 BAN	Cost	Selling Price	Net Margin	Cost	Selling Price	Net Margin	Cost	Selling Price	Net Margin	Cost	Selling Price	Net Margin
Year 1	76.99	74.94	-2.06	79.08	78.34	-0.74	76.13	74.94	-1.19	81.52	83.54	+2.02
Year 2	73.16	72.11	-1.05	74.62	74.13	-0.49	72.34	72.11	-0.23	76.52	77.26	+0.74
Year 3	71.78	75.04	+3.26	71.16	74.97	+3.81	70.97	75.04	+4.07	70.87	75.81	+4.94
Year 4	80.04	84.45	+4.41	77.85	82.76	+4.91	79.14	84.45	+5.31	78.08	83.92	+5.84
Year 5	88.63	85.82	-2.81	86.83	84.39	-2.44	87.63	85.82	-1.81	85.83	84.52	-1.28

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*Data are annual averages based upon animals purchased during the year indicated.

Through the use of cost of production data for cattle feeding operations, together with baseline and drug ban alternatives, prices for slaughter cattle prices, feed prices, etc., net returns per feedlot operator are estimated under both baseline, moderate and high ban alternatives. Under the selected drug ban scenarios, net returns per operator increased over baseline projections, page 21.

Pork

As illustrated in table 2, the pork production process is much more dependent upon subtherapeutic use of animal drugs. Initial technological impacts on production were estimated at -4.9% and -17.8% under moderate and high efficacy levels, table 2.

Our analysis indicates that the demand for pork is even more price inelastic than beef. Thus, the initial reduction in pork output resulted in a much larger increase in pork prices. Even in the first year beef producers do have an opportunity to respond to higher hog prices; pork output thus declined by 3.2% and 15.6% under moderate and high efficacy, respectively, table 3. Hog prices as a result rose 7.2% and 35.1%, respectively. Under the high efficacy scenario, hog prices would average $57/cwt. during year one, versus the baseline expectation of $42/cwt.; by the second year hog prices would be forecast to reach nearly $65/cwt., versus $53/cwt. in the baseline, table 4. To the consumer, average retail pork prices increased to average $1.74/lb. under the high scenario, 27¢/lb. above baseline during year one.

Under the assumption of moderate efficacy, hog prices rose enough to induce hog products to boost production from the initial 4.9% decline

TABLE 8

COST OF PRODUCTION AND NET RETURNS TO CORN BELT HOG FEEDING*

	No Ban			Ban					
				Moderate Efficacy			High Efficacy		
	Cost	Selling Price	Net Margin	Cost	Selling Price	Net Margin	Cost	Selling Price	Net Margin
	$/cwt.								
HISTORY									
1976	43.49	40.69	+2.80						
1977	41.94	44.14	+2.20						
1978	48.40	49.51	+1.11						
1980 BAN									
Year 1	44.91	42.28	-2.63	47.98	46.72	-1.26	56.40	58.05	+1.65
Year 2	51.97	55.89	+3.92	53.27	58.77	+5.51	60.02	66.67	+6.65
Year 3	59.76	61.86	+2.10	59.89	63.37	+3.48	64.38	68.10	+3.72
Year 4	61.52	65.79	+4.27	61.74	67.23	+5.49	66.24	72.25	+6.01
Year 5	63.55	65.80	+2.25	64.32	66.70	+2.38	68.88	72.36	+3.48

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*Data are based upon animals purchased during the year indicated.

to a 1% decline from baseline by year three, and under this scenario production remains approximately 1% below baseline for the remaining fourth and fifth years. Hog prices by the third year increased 2.7% above baseline. This percentage increase in prices decelerated to 1.3%-1.9% during the remaining two years, as supplies leveled off.

Under the assumption of high efficacy, pork output was still 6.7% below baseline in year three and did not improve during the following years, with production remaining 6%-8% below baseline, table 3. Thus, hog prices under this scenario are 10%-11% above baseline even during year three. Hog prices during years four and five remained approximately 9% above the baseline production, table 4. Thus, during the fourth and fifth years, retail pork prices to consumers averaged $2.24/lb., approximately 6% above baseline.

Poultry and Eggs

The poultry industry is more dependent upon the subtherapeutic use of animal drugs than any other sector, as shown by the estimated moderate and high efficacy production impacts in table 2. Under the assumption of moderate efficacy, broiler and turkey output is initially reduced by 8.3% and 6.1%, respectively.

Again, because of the inelastic nature of demand for these products their prices responded dramatically to changes in output. During the first year wholesale broiler and turkey prices rose by 12% and 6% with moderate efficacy and 25% and 16% with high efficacy, respectively, table 4.

Sharply higher broiler prices provided the economic incentives to increase production from these initial levels to -4.6% by year three assuming moderate efficacy and to a decline of 12% from baseline assuming high efficacy. By this third year broiler prices still averaged 7.5% and 13%, respectively, above baseline. Under the moderate efficacy scenario broiler output by year four remained approximately 4% below baseline, a percentage which remained during the fifth year, table 3. And thus, broiler prices during the fourth and fifth years averaged 5% above baseline levels, table 4.

Assuming high efficacy, broiler output "settles" at approximately 10% below baseline during the fourth and fifth years of the simulation. As a result broiler prices averaged 59¢-60¢/lb., 10%-11% above baseline. Thus, five years after the ban, retail prices are expected to average nearly 90¢/lb., 6¢ or 7%-8% above the baseline.

Assuming moderate efficacy the impact upon turkey production leveled off at -3.5% by the third year and fell -3.1% by year five. Assuming high efficacy, however, turkey production dropped by 9% by the third year and continued close to this percentage through the remainder of the simulation period.

Turkey prices are somewhat more elastic than the other commodities in question, and thus price changes relative to volume changes are smaller. However, as indicated above, the volume output changes are quite large. Thus during the fourth and fifth years, turkey prices averaged 3%-4% above baseline under the moderate scenario and 9% under the high scenario.

The estimated technological impacts on egg production at -1.7% and -3.6%, table 2, are small relative to pork, broilers and turkeys. Thus, even though egg supplies are initially reduced, egg prices were boosted by the combined factors of smaller egg supplies, and reduced supplies and

TABLE 9

COST OF PRODUCTION AND NET RETURNS TO BROILER PRODUCERS*

	No Ban			Ban					
				Moderate Efficacy			High Efficacy		
	Total Cost	Selling Price	Net Margin	Total Cost	Selling Price	Net Margin	Total Cost	Selling Price	Net Margin
	¢/lb.								
HISTORY									
1976	39.4	40.2	+0.9						
1977	40.5	40.9	+0.4						
1978	39.8	44.6	+4.8						
1980 BAN									
Year 1	44.33	42.87	-1.46	46.45	48.18	+1.73	48.54	53.80	+5.26
Year 2	45.39	46.94	+1.55	46.94	51.74	+4.80	48.10	56.70	+8.60
Year 3	47.28	54.20	+6.92	49.21	58.24	+9.03	51.41	61.33	+9.92
Year 4	48.98	52.56	+3.58	51.42	55.27	+3.85	54.18	58.24	+4.06
Year 5	50.34	55.21	+4.87	53.11	58.01	+4.90	56.46	61.00	+4.55

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*Data are annual averages.

higher prices of all meat and fowl. Producer price increases of 7.3% and 15.6% under the moderate and high scenarios, respectively, improved profits significantly enough to return production near the baseline levels by the second year of the ban. By the second year, egg output is estimated at only 0.4% below baseline under the moderate scenario and 0.4% above baseline under the high scenario.

Smaller supplies and higher prices for meat products increased egg prices 2.0% to 3.0% above baseline during the last three years of the simulation assuming moderate efficacy and 4% to 5% above baseline assuming high efficacy. Thus, retail egg prices to consumers four to five years following a ban averaged approximately 1.9% above baseline assuming moderate efficacy and 3.5% above baseline assuming high efficacy.

Animal Feeds

Reduced livestock production under both scenarios reduced domestic demand for feed grains[1] and high protein meal. Of course, production of feed grains and soybeans[2] is annual with only one crop grown per year. Thus any immediate reduction in domestic use caused inventories of these commodities to increase.

Assuming moderate drug efficacy, domestic consumption of corn and soybean meal declined 0.9% and 4.2% during the first two crop years of the ban (fall 1979 to summer 1981). Soybean meal is more heavily impacted than corn because the poultry sector is the hardest hit by the animal drug ban, and this sector is a primary consumer of meal. Under the moderate scenario, soybean meal prices fell 7% below baseline during the first two crop years. Since soybean crushings are reduced, thus decreasing the supply of soybean oil as well as meal, soybean oil prices would be expected to rise. However, the decline in meat prices more than offset the advance in oil prices to reduce the price of soybeans to growers by 3.7% during this period.

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[1] Includes corn, grain sorghum, oats and barley.

[2] Soybeans are crushed to yield approximately 79% meal, 18% oil and 3% by-product on a per pound basis. Soybeans account for 75% of total U.S. high protein meal.

A weakened soybean market reduced planted soybean acreage by 1.2% from baseline in the 1980 growing season and 2.8% in 1981 as producer responses mature and soybean inventories continue to build. By the fourth and fifth years of the analysis soybean acreage averaged approximately 1%, or 595 thousand acres below baseline, and soybean prices averaged 0.5% below baseline.

The corn market under the moderate scenario suffered 1.0% and 0.7% declines, respectively, in domestic demand during the first two crop years of this analysis before increasing in year five.

Reaction patterns in the crop sector to the high drug efficacy scenario are similar to those in the moderate scenario, but at much more significant levels. Initially, soybean meal prices fall 11% and 24% below baseline during the first two crop years. This depressed soybean prices by 5.6% and 13.5%, respectively. As a result of lower soybean prices growers by year three reduced soybean acreage by 6.4% or 4,350 thousand acres. By the fifth year soybean prices averaged 2% below baseline with U.S. acreage 1.8% below baseline.

Corn prices by the second and third years would be expected to decrease by 5.0%-5.5% below baseline as inventories build due to reduced domestic

TABLE 10

CORN DEMAND AND SUPPLY PROJECTIONS AND PERCENTAGE CHANGES FROM BASELINE PROJECTIONS FOR FIVE YEARS AFTER BAN OF SELECTED ANIMAL DRUGS BEGINNING IN 1980, MODERATE AND HIGH EFFICACY

	Year[a]				
	1	2	3	4	5
	Moderate Efficacy				
Price, Chicago, $/bu.	2.79	2.80	2.95	3.09	3.21
% change	-0.32	-2.06	-3.04	-1.67	-1.48
Domestic Consumtpion, bil. bu.	4.70	4.82	4.89	5.12	5.32
% change	-1.02	-0.71	-0.34	-0.30	0.17
Acreage Harvested, mil.	69.53	70.22	72.37	72.00	72.27
% change	0.0	0.09	0.12	-0.56	-0.45
Production, bil. bu.	6.67	6.81	7.38	7.56	7.80
% change	0.0	0.09	0.12	-0.56	-0.45
Inventory,[b] bil. bu.	1.15	0.85	0.94	0.90	0.89
% change	4.43	11.7	13.86	10.71	5.09
	High Efficacy				
Price, Chicago, $/bu.	2.77	2.70	2.89	3.15	3.29
% change	-1.08	-5.55	-4.96	0.26	0.85
Domestic Consumption, bil. bu.	4.62	4.76	4.97	5.15	5.28
% change	-2.70	-2.08	1.23	0.18	-0.44
Acreage Harvested, mil.	69.53	70.36	73.24	70.60	71.59
% change	0.0	0.28	1.32	-2.50	-1.38
Production, bil. bu.	6.67	6.82	7.47	7.41	7.73
% change	0.0	0.28	1.32	-2.50	-1.38
Inventory,[b] bil. bu.	1.23	1.21	1.11	0.90	0.85
% change	11.68	58.79	34.44	10.55	0.21

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[a] Crop year basis, year 1 is 1979/80

[b] Crop year ending inventory, September 30

TABLE 11

SOYBEAN MEAL AND SOYBEANS DEMAND AND SUPPLY PROJECTIONS AND PERCENTAGE CHANGES FROM BASELINE PROJECTIONS FOR FIVE YEARS AFTER BAN OF SELECTED ANIMAL DRUGS BEGINNING IN 1980, MODERATE TO HIGH EFFICACY

	Year[a]				
	1	2	3	4	5
	Moderate Efficacy				
Soybean Meal					
Price, Decatur, $/ton	180.14	167.63	182.20	197.29	198.45
% change	-4.51	-9.28	-5.39	-2.78	-1.02
Domestic Consumption, mil. tons	17.8	18.2	18.9	19.6	20.8
% change	-4.93	-3.61	-3.53	-1.90	-1.47
Soybeans					
Price, Chicago, $/bu.	6.75	6.45	7.12	7.85	7.63
% change	-2.14	-5.22	-2.62	-1.11	-0.10
Domestic Crushings, bil. bu.	1.05	1.09	1.10	1.17	1.22
% change	-2.67	-2.15	-2.05	-1.29	-1.04
Acreage Harvested, mil.	70.6	66.3	66.0	69.15	72.44
% change	0.0	-1.16	-2.76	-1.23	-0.45
Production, bil. bu.	2.07	1.96	2.00	2.14	2.30
% change	0.0	-1.16	-2.76	-1.23	-0.45
Inventory,[b] mil. bu.	290.	214.	126.	91.	122.
% change	11.08	16.23	-2.74	-14.08	-9.42
	High Efficacy				
Soybean Meal					
Price, Decatur, $/ton	167.90	141.07	168.36	180.46	190.07
% change	-11.00	-23.65	-12.57	-11.08	-5.20
Domestic Consumption, mil. tons	16.8	17.3	18.1	19.0	20.1
% change	-10.62	-8.62	-7.26	-5.05	-4.60
Soybeans					
Price, Chicago, $/bu.	6.51	5.88	6.82	7.46	7.48
% change	-5.56	-13.54	-6.76	-6.07	-2.05
Domestic Crushings, bil. bu.	1.01	1.05	1.07	1.14	1.20
% change	-6.46	-5.96	-5.36	-3.79	-3.05
Acreage Harvested, mil.	70.6	65.5	63.5	68.3	71.47
% change	0.0	-2.42	-6.40	-2.46	-1.79
Production, bil. bu.	2.07	1.93	1.92	2.12	2.27
% change	0.0	-2.42	-6.40	-2.46	-1.79
Inventory,[b] mil. bu.	330.	273.	147.	115.	139.
% change	26.81	48.17	13.53	8.41	3.86

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[a] Crop year basis, year 1 is 1979/80

[b] Crop year ending inventory, July 31

consumption and slight increases in corn acreage. By the fourth year, however, corn acreage would be expected to be cut back by 2.5%, or 1,810 thousand acres from baseline, in order to bring corn inventories back into line. Reduced production, similar inventories, actual increases from baseline in cattle feeding and sharply higher livestock prices would be expected to offset reduced corn demand from the poultry and hog sectors to return corn prices to baseline levels (within 1%) by the fourth and fifth years.

Farm Income

The index of prices received by farmers for livestock products during the first year of a ban increases by 5.3% under the moderate scenario and 14.9% under the high scenario. These higher prices more than offset the decline in volume output to result in an increase in total livestock cash receipts of 3.4%, or $2.4 billion, and 7.9%, or $5.7 billion, assuming moderate and high efficacies, respectively, table 12. By the fifth year, however, livestock cash receipts fell to baseline levels assuming moderate efficacy. Assuming high efficacy, livestock cash receipts still were 1.3%, or $1.3 billion above baseline in the fifth year.

Although prices and cash receipts to livestock producers increased under these scenarios, prices and receipts to the agricultural crop sector are reduced. Because of the annual and seasonal nature of crop production the most significant calendar year impact to crop prices and receipts would occur during 1981. During 1981, crop prices under the moderate and high scenarios fell 1.4% and 3.5%, respectively. By the fifth year, the index of all crop prices returned to near baseline levels under both scenarios.

TABLE 12

TOTAL FARM CASH RECEIPTS AND TOTAL NET FARM INCOME PROJECTIONS AND PERCENTAGE CHANGES FROM BASELINE PROJECTIONS FOR FIVE YEARS AFTER BAN OF SELECTED ANIMAL DRUGS BEGINNING IN 1980 MODERATE AND HIGH EFFICACY

	Year				
	1	2	3	4	5
	billion dollars				
	Moderate Efficacy				
CASH RECEIPTS					
Livestock	74.5	77.4	79.7	89.4	96.6
% change	3.4	2.8	1.4	0.4	-0.0
$ change	2.4	2.1	1.1	0.3	-0.0
Crops	61.8	65.0	70.6	75.7	82.1
% change	-0.6	-1.2	-1.1	-0.4	0.1
$ change	-0.4	-0.9	-0.8	-0.3	0.1
TOTAL	136.3	142.4	150.4	165.1	178.7
% change	1.5	0.9	0.2	0.0	0.0
$ change	2.0	1.3	0.3	0.1	0.0
NET FARM INCOME	30.9	31.9	35.3	38.6	42.3
% change	9.7	6.3	1.9	0.7	-0.6
$ change	2.7	1.9	0.7	0.3	-0.2
	High Efficacy				
CASH RECEIPTS					
Livestock	77.8	80.1	81.3	90.3	97.8
% change	7.9	6.4	3.4	1.4	1.3
$ change	5.7	4.8	2.6	1.3	1.3
Crops	60.7	63.4	69.8	74.9	81.8
% change	-2.4	-3.6	-2.3	-1.5	-0.3
$ change	-1.5	-2.3	-1.7	-1.1	-0.3
TOTAL	138.5	143.5	151.1	165.2	179.6
% change	3.1	1.8	0.7	0.1	0.6
$ change	4.2	2.5	1.0	0.2	1.0
NET FARM INCOME	34.8	34.4	37.4	39.8	44.6
% change	23.5	14.8	7.9	3.8	4.8
$ change	6.6	4.4	2.7	1.4	2.1

Crop cash receipts to farmers during 1981 dropped 1.2% or $900 million below baseline assuming moderate efficacy, and 3.6% or $2,300 million assuming high efficacy, table 12. During the fifth year, crop cash receipts were 0.3% or approximately $300 million below baseline under the high scenario.

Thus, total receipts to livestock farmers increased while total receipts to crop farmers declined. Because the increase in livestock receipts is greater than the decline in crop receipts, total farm cash receipts increased over the entire five-year period under both scenarios, table 9.

U.S. Economy

Reduced available supplies of meat and poultry mean higher food prices for consumers. With retail prices increasing 7¢/lb. for beef, 8¢/lb. for pork, and 6¢/lb. for chicken (year one of moderate scenario) for example, the Consumer Price Index (CPI) for food increases by 1.3%, thus increasing total dollars spent on food and beverages by $1.7 billion, or 0.5%. The overall CPI would be expected to rise 0.3% over baseline during the first two years, with this change decelerating to 0.1% by the fourth year. This increase in food inflation, for example, reduced consumption of durable goods by 0.8% or $0.1 billion in year two. Weaker consumer spending power thus increased the unemployment rate by 0.4% in year one and 1.1% in year two. This factor combined with a higher inflation rate reduced real disposable personal income by $0.4 billion in year one and $1.5 billion, or 0.1% in year two as the negative impacts rippled through the economy, table 14, and impacted other industries.

TABLE 13

INDEX OF ALL PRICES RECEIVED BY FARMERS AND INFLATION RATE PROJECTIONS AND PERCENTAGE CHANGES FROM BASELINE PROJECTIONS FOR FIVE YEARS AFTER BAN OF SELECTED ANIMAL DRUGS BEGINNING IN 1980
MODERATE AND HIGH EFFICACY

	Year				
	1	2	3	4	5
			1967=100		
	Moderate Efficacy				
Prices Received by Farmers	255	264	273	295	314
% change	3.0	2.1	0.6	-0.1	-0.5
WPI, Farm Prod, Processed Foods & Feeds	248	261	275	294	313
% change	1.5	0.9	0.3	-0.0	-0.2
CPI, Food	257	275	294	316	340
% change	1.3	1.2	0.6	0.2	-0.1
CPI, All Items	238	257	275	296	317
% change	0.3	0.4	0.2	0.1	0.0
	High Efficacy				
Prices Received by Farmers	268	273	278	298	320
% change	8.4	5.7	2.7	1.1	1.3
WPI, Farm Prod, Processed Foods & Feeds	255	265	277	296	316
% change	4.1	2.7	1.1	0.6	0.8
CPI, Food	263	281	298	319	343
% change	3.7	3.5	1.7	0.9	0.9
CPI, All Items	240	258	277	296	318
% change	0.9	1.0	0.6	0.4	0.3

TABLE 14

MAJOR ECONOMIC INDICATORS, PROJECTIONS AND PERCENTAGE CHANGES FROM BASELINE PROJECTIONS FOR FIVE YEARS AFTER BAN OF SELECTED ANIMAL DRUGS BEGINNING IN 1980, MODERATE AND HIGH EFFICACY

	Year				
	1	2	3	4	5
	Moderate Efficacy				
CPI, All Items, 1967=100	235	253	270	288	308
% change	+0.3	+0.3	+0.2	+0.1	-0.0
Real GNP, 1972$	1411	1455	1515	1579	1624
% change	-0.1	-0.2	-0.2	-0.1	-0.1
Unemployment Rate	7.69	7.48	6.45	5.42	5.11
% change	+0.4	+1.1	+1.6	+1.5	+1.1
absolute change	+0.03	+0.08	+0.10	+0.08	+0.05
	High Efficacy				
CPI, All Items, 1967=100	236	254	271	289	308
% change	+0.8	+0.9	+0.6	+0.3	+0.2
Real GNP, 1972$	1409	1449	1509	1573	1618
% change	-0.3	-0.6	-0.6	-0.5	-0.5
Unemployment Rate	7.74	7.65	6.63	5.58	5.25
% change	+1.2	+3.3	+4.4	+4.5	+3.8
absolute change	+0.09	+0.24	+0.28	+0.24	+0.18

Aside from the expected differences in the output of livestock, poultry and eggs, and meat products, the ban would be expected to produce noticeable decreases in the constant dollar (real) output of other sectors. In the transportation sectors, a decline in constant dollar output compared with the baseline would also be expected, reflecting not only reduced demand for transportation services to haul the meat products themselves, but also the lowered demand for transporting livestock to slaughter yards, grain to feedlots, etc. Railroad output would decline 0.3% in 1980 while trucking and warehousing output would decline 0.4%; these effects trail off to a 0.1% decline from the standard by 1984.

Not all the production effects are negative, however. The product shipments of dairy products, canned and frozen foods, and bakery products all rise as a result of changing patterns in food consumption triggered by the increased relative prices of meat products to other foodstuffs. In nearly every sector, however, the total effect of the ban results in a decline in real output of between -0.1% and -0.4% in the initial year of the ban, trailing off to near zero by 1984. The more important sectors are highlighted in table 15.

As noted above the imposition of the proposed ban results in a 0.4% higher unemployment rate than in our baseline scenario in the first year, and a 1.1% higher rate in the second year. Agricultural employment comprises 2917 thousand jobs in the moderate impact scenario, which is 1% less than the baseline; in year two agricultural employment is 1.2% lower than the baseline. By the fifth year, agricultural employment increases to 2516 thousand jobs, 0.2% lower than the baseline. Employment by the meat products industry, at 332 thousand jobs in year one, represents

TABLE 15

INDUSTRY PRODUCT-SHIPMENTS AND PERCENTAGE CHANGES FROM BASELINE PROJECTIONS FOR FIVE YEARS AFTER BAN OF SELECTED ANIMAL DRUGS BEGINNING IN 1980, MODERATE AND HIGH EFFICACY
(output in millions of 1976$)

	Year				
	1	2	3	4	5
	---------------- Moderate Efficacy ----------------				
Meat Products	43663	44309	46462	47534	48880
% change	-2.6	-1.8	-1.2	-0.6	-0.4
Railroads	23981	24436	25481	26525	27072
% change	-0.3	-0.4	-0.3	-0.1	-0.1
Trucking & Warehousing	49274	51170	53568	56012	57563
% change	-0.4	-0.4	-0.3	-0.1	-0.1
Wholesale Trade	172590	178522	186925	196162	202396
% change	-0.2	-0.3	-0.2	-0.1	-0.1
Retail Trade	233508	241050	252846	265263	273731
% change	-0.1	-0.2	-0.2	-0.0	-0.1
	---------------- High Efficacy ----------------				
Meat Products	41146	42454	44851	46393	47677
% change	-8.2	-5.9	-4.7	-3.0	-2.8
Railroads	23847	24272	25341	26392	26938
% change	-0.8	-1.0	-0.8	-0.6	-0.6
Trucking & Warehousing	48876	50730	53202	55674	57229
% change	-1.2	-1.3	-1.0	-0.7	-0.7
Wholesale Trade	171954	177603	186112	195283	201559
% change	-0.6	-0.8	-0.7	-0.5	-0.5
Retail Trade	232895	240084	252011	264097	272661
% change	-0.4	-0.6	-0.5	-0.5	-0.5

a decline of 1.5%, or nearly 5,000 jobs, from the baseline scenario. Employment by the trucking and warehousing industry would be 0.2% less than in the standard, or about 3,000 during the first year. The employment differences between standard and moderate dwindle to nearly zero by 1984.

Assuming high efficacy, the overall CPI increased 0.8% in the first year and 0.9% in year two. Five years following the ban the overall CPI averaged 0.2% above baseline. Real disposable personal income declined by $1.7 billion in year one and $5.1 billion in year two. This decline, however, decelerated little, remaining 0.5% below baseline during the fifth year. The reduction in real GNP would be expected at 0.3% in year one growing to 0.6%, or $8.1 billion (1972$). Under the assumption of high drug efficacy, real GNP by the fourth and fifth years would be expected to total 0.5% below baseline, equivalent to $8.0-$8.4 billion (1972$) in lost national output.

Stronger impacts would also be felt in the transportation sectors, where railroad output would decline by 0.8% and trucking output by 1.2%. Both wholesale and retail trade output would be considerably lower in the higher impact scenario, with constant dollar output from these sectors respectively 0.6% and 0.4% lower than baseline in 1980. In general, the first year impact on individual industries ranges from -0.2% to -0.9% in comparison to the standard.

The unemployment rate increased by 1.2% and 3.3% in years one and two, translating to an increase in unemployment of approximately 90,000 and 260,000 thousand people, respectively. For example, in 1980 agricultural employment is 3.0% lower than in the baseline scenario. Employment in the meat products industry, at 321 thousand in 1980, represents a 4.7% decline from the baseline scenario, trailing off to a 1.2% lower level compared to the baseline in 1984.

As with the moderate scenario, the net effect of the proposed ban would be an increase in unemployment, with the impact being most strongly felt in the agriculture and meat products sectors. Some industries would have a slight increase in employment; overall, however, the effect would be one of a net loss in jobs.

TABLE 16

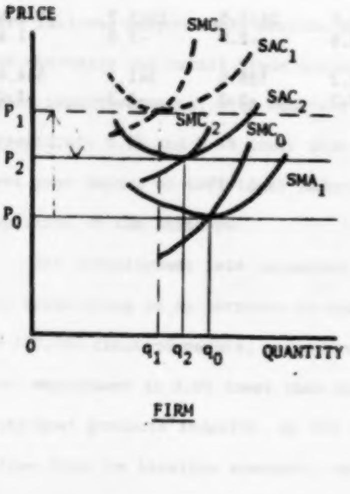
EMPLOYMENT BY INDUSTRY (THOUSANDS OF JOBS) AND PERCENTAGE CHANGES FROM BASELINE PROJECTIONS FOR FIVE YEARS AFTER BAN OF SELECTED ANIMAL DRUGS BEGINNING IN 1980, MODERATE AND HIGH EFFICACY

	Year				
	1	2	3	4	5
	Moderate Efficacy				
Agriculture	2917.0	2777.5	2667.7	2585.3	2515.8
% change	-1.0	-1.2	-0.9	-0.4	-0.2
Meat Products	331.8	337.8	344.9	344.9	347.8
% change	-1.5	-0.9	-0.5	-0.2	-0.1
	High Efficacy				
Agriculture	2857.8	2710.7	2613.0	2543.7	2479.9
% change	-3.0	-3.6	-2.9	-2.0	-1.6
Meat Products	320.7	330.2	339.0	341.3	344.0
% change	-4.8	-3.2	-2.2	-1.3	-1.2

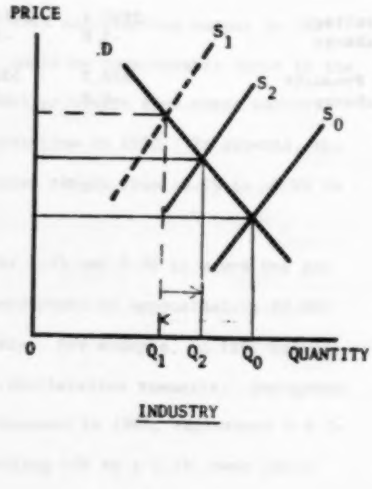
APPENDIX A

THEORETICAL FRAMEWORK

In a competitive economic environment, both the individual firm and the industry are assumed to be in a state of equilibrium at price P_0 and quantities q_0 and Q_0, respectively, as shown in the diagram below. Individual firms (hog producers, feedlot operators, broiler growers, etc.) are producing quantity q_0 at price P_0 at the lowest point on the average cost curve (SAC_0). The supply curve for the industry (total pork, beef or broiler, etc.) can be achieved by summing the marginal cost curves (SMC_0) of all the individual producers. This summation results in the supply curve S_0. The intersection of this supply with a given demand curve results in an equilibrium price of P_0, with an industry supply of Q_0.


PRICE
SMC_1
SAC_1
SAC_2
P_1
SMC_2
SMC_0
P_2
SMA_1
P_0
0
q_1
q_2
q_0
QUANTITY

FIRM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QUANTITY

INDUSTRY

Imposing a ban on subtherapeutic drug use in animal feeding would subsequently cause an increase in inputs required to produce the same unit of output, due to poorer feed conversion, increased death losses, etc., thus increasing producers' costs and shifting the cost functions upward to SMC_1 and SAC_1. Higher average cost curves and steeper marginal cost curves would result in upward movement of each firm's cost functions to above the pre-ban level to SAC_1 and SMC_1 with output adjusting downward to q_1.

Summing the new marginal cost curve yields a new industry supply curve, S_1, which has shifted to the left of the pre-ban industry supply curve, S_o. This leftward movement of supply along the same demand schedule results in a new equilibrium price P_1 at a lower quantity Q_1.

Initially the market is in disequilibrium at P_1 and Q_1 since the immediate decline in output is due to a removal of an input which reduces output by specified technological factors. The impact on price of this smaller supply will depend upon the price elasticity of demand for the products in question. Because livestock products have been found to have relatively inelastic demand, i.e. the percent change in quantity demanded due to a 1% change inprice is less than 1%, or the demand curve is fairly "steep" versus "flat," the percentage change in price will exceed the percentage change in quantity. Thus, total revenue to the producer should rise. Increases prices and revenue are necessary to prompt producers to increase production from initially reduced levels (q_1 and Q_1) back "towards" the pre-ban level of production (q_2 and Q_2). The key questions to be addressed in this study are to quantify where the supply curve finally settles based upon a new product price-product cost situation, the "path" the supply curve, i.e. S_2, takes to settle to a new equilibrium situation (P_2 and Q_2), and the price, market and economic repercussions of this new equilibrium.

Initially, with the imposition of a ban on selected animal drugs, meat output falls (the supply curve is shifted to the left) and consumers are offered a reduced volume of meat and meat products. Subsequently, consumers will bid up the prices of these products in an attempt to maintain consumption and fulfill demand. The market price response, naturally, varies between products, depending upon the magnitude of the supply change, the price elasticity of demand of that product, as well as the magnitude of and cross elasticities of other impacted competing products. Thus, for example, cattle prices would be expected to rise due directly to the reduction in beef supplies, and also due to the positive cross elasticities from a reduced supply of pork and poultry. Similarly, any particular product price change is the result of both direct and cross elasticity responses.

Because of the relatively inelastic nature of meat product prices, higher consumer prices for beef, pork, poultry and eggs will cause not only an increase in food inflation, but more importantly an increase in total consumer expenditures for food. With consumers spending more disposable income for food, spending on other discretionary items would decline, eventually causing reduced production and lower employment in those sectors.

Higher meat and meat product prices at the producer level pose a new economic situation for the livestock producer and, consequently, ultimately influence future production. However, under a ban scenario, there is yet another critical influence on future production, namely feed costs.

With the initial dramatic reduction in livestock output caused by the imposition of a ban, demand for animal feed declines. Feed consumption falls primarily due to the reduction in total animals produced, increased death loss, and feeding to lighter weights. These declines would be expected to more than offset the positive impact upon feed demand from lower feed conversion rates.

Initially, as feed usage (corn, sorghum, oats, barley and high proten meals) declines, inventories of these commodities build and prices decline. Thus, livestock and poultry producers experience some easing on the cost side from lower feed prices. However, supplies of feed grains and soybeans would also be expected to contract as feed grain and soybean producers respond in turn to their lower product prices and reduce planted acreage. Thus, a new equilibrium is met in these grain markets.

Thus, under a ban scenario the livestock producer faces a very different economic situation, an economic situation which presents higher potential profits due to higher product prices and lower feed prices. In fact, total revenue profits on a per unit of output basis would be expected to rise due to the inelastic demand characteristics of the products in question. This higher potential profit inspires producers in future time periods to attempt to return production to pre-ban levels. If per unit profitability did not improve, the decline in total volume output during following periods would exceed the "technological" reduction of the initial impact. Producers need, and would be expected to receive, this additional profit motivation, i.e. above the baseline profit picture, to increase supplies from the reduced initial period. It is the speed at which the producers in question adjust output back toward the baseline equilibrium, as well as the new equilibrium price and output achieved under the ban, which are the key questions of this study.